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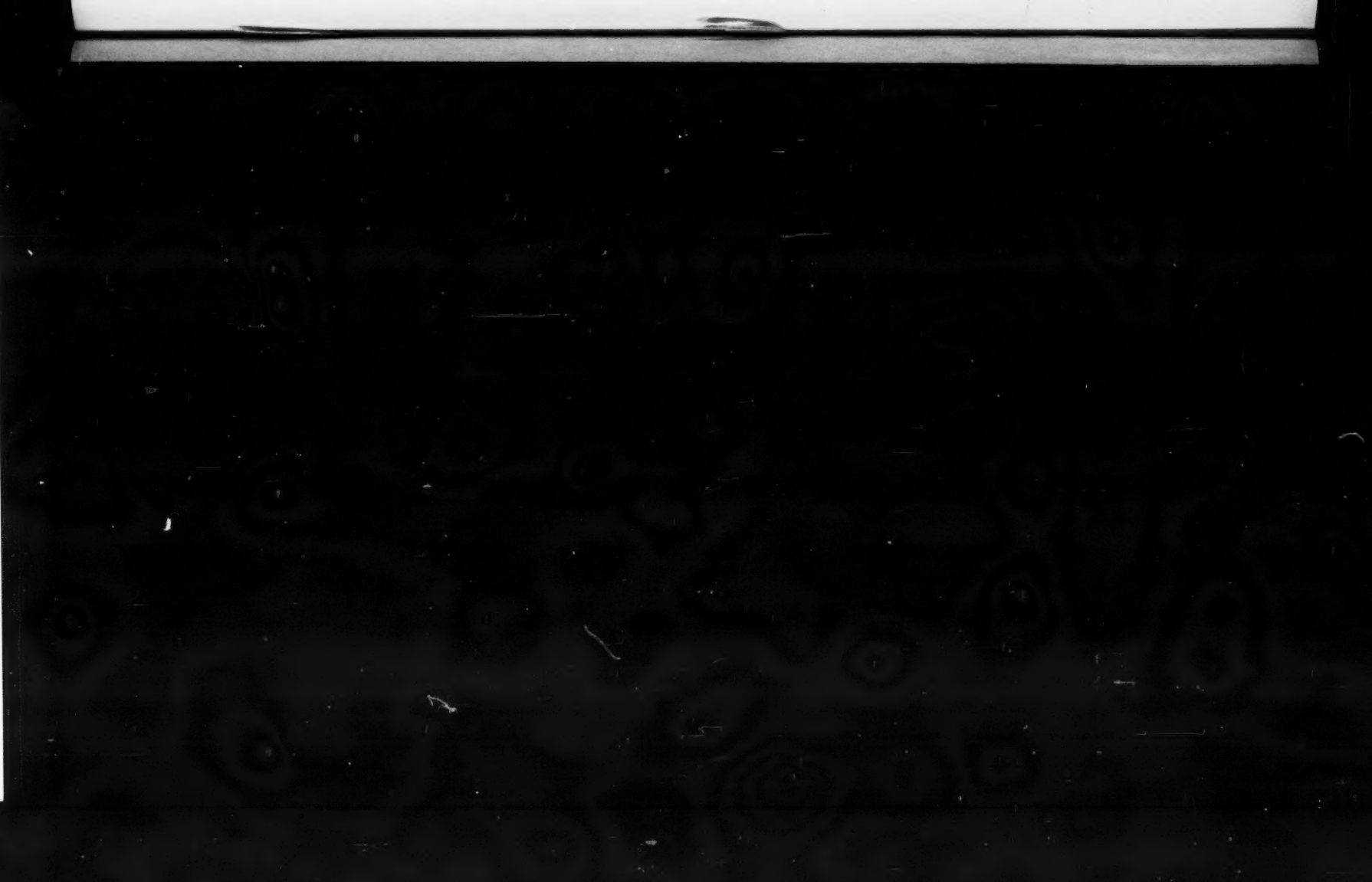

Archives Of Dermatology And Syphilology

VOLUME 59 MARCH 1949 NUMBER 3

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VIRUS AS POSSIBLE ETIOLOGIC AGENT OF ERYTHEMA MULTIFORME EXUDATIVUM, BULLOUS TYPE

Report of a Case

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CONSIDERABLE confusion exists in regard to the etiology and the interrelationship of a variety of clinical entities involving epithelial structures of the body, the lesion common to all of which is thought to be initially of a herpetic nature.

The entities which form this group involve the palpebral conjunctiva of the eyes, the mucous membranes of and the skin about the mouth, anus and genitalia, the mucous membranes of the oropharynx and bowel and occasionally the skin of the entire body. The disease of this general nature which affects the palpebral conjunctiva has been referred to as the Stevens-Johnson syndrome. This condition, described in 1922 by the men whose name it bears,[1] is a severe form of membranous conjunctivitis, associated with gingivostomatitis and generalized eruption of the skin. The presence of fever in cases of this disease led them to suggest the descriptive term "eruptive fever with stomatitis and ophthalmia." The ophthalmic consequences of this disease are serious, leading often to blindness.

In 1866, Hebra[2] described a group of lesions of the skin which he termed "polymorphous erythemas." In this group he included "erythema exudativum multiforme," an entity characterized by a typical polymorphous cutaneous rash and by constitutional signs and symptoms. He also noted that an occasional patient presented bullae and involvement of the mucous membranes. A review of the literature by Fletcher and

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1. Stevens, A. M., and Johnson, F. C.: New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child **24**:526 (Dec.) 1922.

2. Hebra, F.: On Diseases of the Skin, London, New Sydenham Society, 1866.

Harris[3] revealed that this condition, now commonly referred to as "erythema exudativum multiforme (Hebra) bullous type," was described as early as 1822 by Alibert and Bazin,[3a] reported in 1855 by Jones[4] and again in 1893 by Kaposi.[5] Since that time many reports concerning this entity have appeared in the literature. A variety of descriptive terms have been suggested by the authors. Rendu,[7] observing the involvement of the body orifices, applied the descriptive term *ectodermose erosive pluriodificielle.*

Baader,[8] observing the fever, stomatitis and dermatitis, used the term "dermatostomatitis" and noted the analogy of this disease with the human form of foot and mouth disease. His attempts to prove a virus the etiologic agent were, however, unsuccessful.

A review of the literature to date reveals that the various forms of this condition, involving the skin and mucous membranes, have several clinical features in common. The most striking of these characteristics is the appearance of a vesicular lesion early in the course of the disease. This may occur in the mouth or on the mucous membrane of the palpebral conjunctiva of the eye and is soon associated with similar vesicular lesions of the other mucous membranes of the body or of the skin. In one form of the disease the lesions confine themselves to the mouth, in another to the eyes and mouth and in others to the mouth and penis and/or anus; in the severe forms they spread to the mouth, eyes, penis, anus and the skin of the entire body. The lesions may initially be small and vesicular, developing rapidly into a membranous lesion on an inflammatory base. In the more extensive forms of the disease the lesions, which develop into bullae, are of a pemphigoid nature. Other features frequenty noted are acute onset of a febrile nature, constitutional signs and symptoms, predominance of patients under the age of 15 years and leukopenia in about 30 per cent of the reported cases.

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3. Fletcher, M. W. C., and Harris, R. C.: Erythema Exudativum Multiforme (Hebra)—Bullous Type: Cases Seen in Contagious Disease Hospital, J. Pediat. **27**:465 (Nov). 1945.

3a. Alibert and Bazin, cited by Beaudonnet, B.: Contribution à l'étude des manifestations oculaires deérythème polymorphe, Thesis, Paris, no. 354, Paris, Henri Jouve, 1894.

4. Jones, T. W.: Principles and Practice of Ophthalmic Medicine and Surgery, ed. 2, London, J. Churchill, 1855.

5. Kaposi, M.: Pathologie und Therapie der Hautkrankheiten, ed. 4, Vienna, Urban & Schwarzenberg, 1893.

7. Rendu, R.: Sur un syndrome caracterisé par l'inflammation simultanée de toutes les muqueuses externes (conjonctivale, nasale, linguale, buccopharyngée, anale et balano-preputiale) coexistant avec une éruption varicelliforme puis purpurique des quatre membres, Rev. gén. de clin. et de thérap. **30**:351, 1916.

8. Baader, E.: Dermatostomatitis, Arch. f. Dermat. u. Syph. **149**:261, 1925.

Epidemiologic aspects of erythema multiforme exudativum have been reported. Rigler[9] described an epidemic in Turkey in 1852. Duhring,[10] in 1896, reported 105 cases of an epidemic nature. Guy[11] described a similar epidemic in 1918. More recently, in 1935, Leipner[12] described an outbreak affecting 30 of the 50 children in a boys' home.

The vesicular or bullous nature of the lesions, the presence of constitutional signs and symptoms and the reported epidemiologic occurrence of certain forms of this condition have suggested to many authors the possibility of a virus as the etiologic agent. However, Baader,[8] Koke,[13] Edgar and Syverton[14] and Crance[15] were unable to demonstrate this.

From a review of the literature an impression is gained that these entities differ predominantly in the site of the initial lesion or in the extent and location of the subsequent lesions. The forms described are similar in many respects, suggesting the possibility of a common etiologic factor. For this reason, the clinical and experimental observations in the following case are presented to support the possibility that a virus is a factor in the pathogenesis of this condition.

REPORT OF CASE

History.—A white boy aged 6½ years was admitted to the pediatric ward of the Salt Lake County General Hospital on Nov. 18, 1945. His father had been discharged from the Army on October 26 and during his trip home had had an attack of herpes labialis. The father stated that this attack was the severest he had ever had—he had been subject to recurrent cold sores in the past—but he apparently was not significantly ill with this episode. He returned home about November 1. On November 14 the son was in apparent good health, attending school as usual. On the next day, November 15, he complained of his eyes hurting and of photophobia. The school teacher sent him home, thinking he had "pink-

9. Rigler, cited by Edmund, C.: Clinical Studies of Endogenous Conjunctiva Affections, Acta ophth., 1935, supp. 7, p. 1.

10. Duhring, E.: Beitrag zur Lehre von den polymorphen erythemen, Arch. f. Dermat. u. Syph. **35**:211, 1896.

11. Guy, W. H.: Erythema Multiforme, J.A.M.A. **71**:1993 (Dec. 14) 1918.

12. Leipner, S.: Epidemic Occurrence of Erythema Exsudativum, Dermat. Wchnschr. **101**:1178, 1935; abstracted, Arch. Dermat. & Syph. **35**:304 (Feb.) 1937.

13. Koke, M. P.: Conjunctivitis in Erythema Exudativium Multiforme: Report of Three Cases, Arch. Ophth. **25**:78 (Jan.) 1941.

14. Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis: Report of Two Cases in Children with Certain Observations on Histopathology and Animal Inoculation, J. Pediat. **12**:151 (Feb.) 1938.

15. Crance, A. M.: Vincent's Disease Associated with Erythema Multiforme-Like Eruption: Report of Case, Arch. Dermat. & Syph. **28**:508 (Oct.) 1933.

eye." His eyes were bloodshot; otherwise he felt well. On November 16 he had fever, with the temperature varying from 102 to 103.5 F. Anorexia developed, and a physician noted small blisters on the lips, on the labial mucosa of the mouth and on the inner aspects of the lower eyelids. The next day, on November 17, the boy became acutely ill. The temperature rose to 105 F. (rectal) and remained at this level. The blisters in the mouth extended to the surface of the tongue and over the buccal mucosa. A diffuse, reddish, measles-like rash began to appear over the entire body. The eyes now had a profuse, purulent discharge, and the patient was unable to open them. He was seen again by his physician,

Fig. 1.—Lesions of the body and desquamation of the skin on the soles.

who prescribed sulfadiazine and penicillin. On the next day, the day of admission to the hospital, November 18, the child was acutely ill, delirious and in a highly toxic condition. The lesions had spread rapidly over the entire body, varying from blotchy discoloration of the skin to maculas and papules and to small vesicles, some of which had coalesced to form large bullae. Examination of the urethral orifice revealed blisters and vesicles on a red, inflammatory base about the meatus. Up to this time the patient had received a total of 7 tablets (7.5 grains [0.487 Gm.] each) of sulfadiazine and 200,000 units of penicillin. There were no complaints referable to the respiratory tract and no gastrointestinal symptoms other than the anorexia.

The past history was essentially normal. The neonatal, postnatal and developmental histories were normal. The patient had had pertussis at the age of 2½ years. There was no history of allergy or previous cutaneous disorders. For the past few weeks the child had been extremely nervous, and his physician had administered ¼ grain (0.026 Gm.) of phenobarbital twice a day. The child had also been receiving a compound of copper and vitamin B complex for about the same length of time.

The family history was essentially noncontributory except for a mild episode of eczema in the mother and the presence of a susceptibility to herpes labialis in the father.

Physical Examination.—On admission the child was acutely ill and highly toxic, with a diffuse, erythematous macular, papular and bullous rash over the entire body. The palms, fingers, soles and toes exhibited massive bullae, which yielded a clear fluid, free of organisms, on direct stain. The eyelids were adherent; the eyelashes were matted together with a yellowish, purulent discharge. An attempt to open the eyes caused sloughing of the skin over the lids. There was a mucopurulent discharge present in both anterior nares. The lips were covered with hemorrhagic crusts, removal of which left shallow, ulcerating lesions. The gums were bleeding and soggy. Ulcerated lesions with overlying thin, dirty grayish membrane covered the oral mucosa and the tongue. The breath was foul. Nuchal rigidity was not present. Percussion and auscultation of the chest revealed no abnormality. The heart presented a slight systolic murmur at the apex; the liver and spleen were not palpable. The penis, especially about the meatus, presented crusted lesions of the glans on a raw, hyperemic base (lesions developed around the anus a few days later). There were no abnormal neurologic signs.

Laboratory Data.—On admission the concentration of hemoglobin was 13.5 Gm. per hundred cubic centimeters of blood. There were 5,800 white blood cells, with a differential count of 72 per cent neutrophils, no eosinophils, 23 per cent lymphocytes and 5 per cent monocytes. Two days later there were 4,300 white blood cells, of which 45 per cent were neutrophils, 13 per cent juvenile forms, 1 per cent eosinophils, 39 per cent lymphocytes and 2 per cent monocytes. The icteric index was 6 units, and the sedimentation rate (Wintrobe method) was 5 mm. in one hour.

Material removed from the bullous lesions of the skin showed no recognizable organisms on direct smear with Gram's staining technic, but on culture grew Staphylococcus aureus, Staphylococcus albus, diphtheroids and Neisseria catarrhalis. Blood cultures, made on several occasions, remained sterile.

The results of agglutination tests for typhoid, parathyphoid, brucellosis and Rocky Mountain spotted fever were negative. The Kahn reaction of the blood was negative.

Examination of the cerebrospinal fluid three weeks after onset of the disease revealed 6 cells per cubic millimeter and 23 mg. of globulin, 48 mg. of sugar and 687 mg. of chloride, per hundred cubic centimeters.

Course of Illness.—For the first twenty-four hours after his admission the lesions on the body progressed rapidly, reaching the extent of complete coalescence of all the vesicular and bullous lesions over the pody. The superficial epithelium could be easily removed, as can be done with a second degree burn. The child remained acutely ill for eight days; the temperature fluctuated between 100 and 104 F. and subsided by lysis at the conclusion of this period. For the first few days the patient was irrational most of the time.

All bullae and vesicles desquamated. The entire epidermis of the hands and feet was eventually lost. All the finger nails and toe nails came off. The mucous membrane of the entire oral cavity and of the tongue sloughed off during the course of the disease.

The eyelids were opened about the eighth day, and examination at that time revealed moderately severe conjunctivitis but no corneal involvement. Vision seemed to be unaffected, although there was pronounced photophobia. Funduscopic examination revealed only mild hyperemia. Cultures of the material from the eyes revealed Staph. aureus (coagulase negative), diphtheroids and small, gram-negative rods.

Most of the lesions on the body and the extremities cleared within four weeks. The new, healed skin was lighter in color than the original skin; consequently, the patient's body presented a mottled appearance. However, scarring was not evident. The crusting lesions about the mouth persisted for several weeks longer. The penile lesions were also evident approximately one month after the patient's discharge from the hospital. The patient was seen in February, approximately three months after the onset of the disease. At that time he still complained of photophobia, and a mild amount of purulent discharge from the eyes occurred from time to time. The palpebral conjunctiva of the eyes still showed a mild inflammatory process and evidences of scarring, with a smooth, glistening appearance. The surface of the tongue was smooth, shiny and relatively free of normal papillary markings.

Treatment.—Therapeutic measures included several transfusions of whole blood, administration of plasma and the parenteral administrations of fluids and amino acids during the acute phase of the disease. Penicillin was given intramuscularly in daily doses of 200,000 units for the first two and one-half weeks. In addition to the transfusions and the plasma, 25 cc. of gamma globulin was given on the third day of hospitalization. Moist packs were used over the entire surface of the body as long as there were desquamation and crusting. Local therapy to the eyes consisted of the application of an ointment containing sulfadiazine; this was later changed to an ointment containing penicillin.

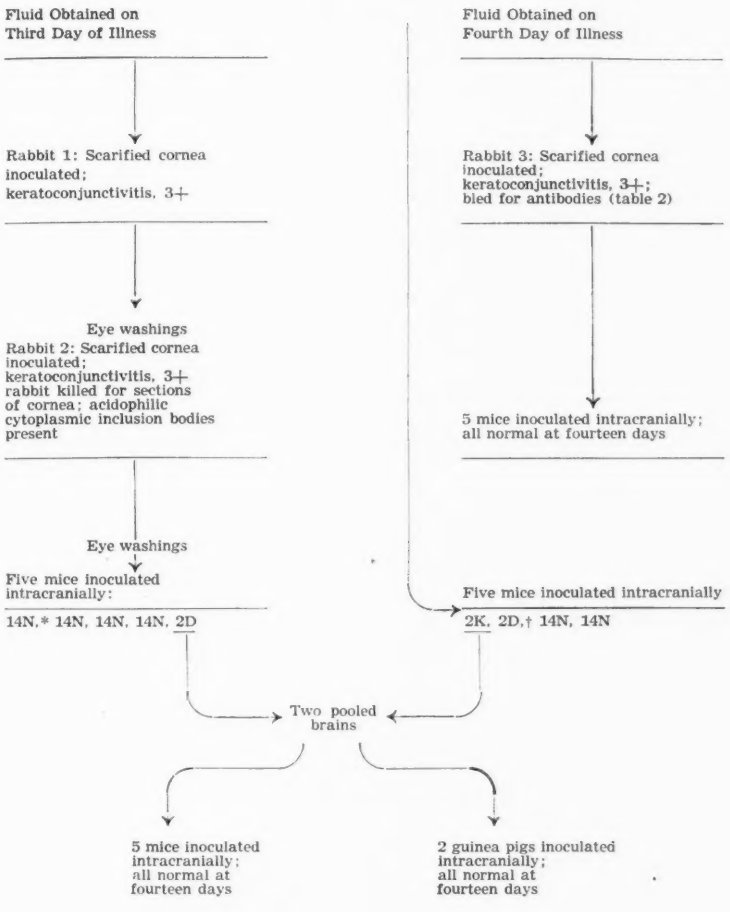
Experimental Data.—Virus Studies of Fluid from Cutaneous Vesicles: Table 1 presents an outline of the procedures followed with material from the vesicles of the skin on the third and fourth days of the patient's illness. The scarified cornea of a normal rabbit was inoculated with the material obtained from the vesicles on the third day of illness. A severe keratoconjunctivitis developed within forty-eight hours. The affected eye was then washed with 0.5 cc. of sterile Ringer's solution. The scarified cornea of a second rabbit was then inoculated with these washings, which were aerobically sterile. Keratoconjunctivitis developed likewise in this rabbit; the animal was then killed and the eye removed for histologic study.

The scarified cornea of a third normal rabbit was inoculated with some of the fluid obtained from the vesicles on the fourth day of illness. This rabbit, too, had a severe keratoconjunctivitis. Some of this fluid was used for intracranial inoculation of 5 Swiss mice. One of these mice was found dead at the end of forty-eight hours but was unfit for use in further passage. A second mouse, showing slight neurologic involvement, was killed in forty-eight hours. The brain of this mouse was removed and pooled with the brain of the mouse that had died of the intracranial inoculation of washings from the infected cornea of rabbit 2, mentioned in the preceding paragraph (table 1). An emulsion of the brains of

these 2 mice was injected intracerebrally into 5 mice and 2 guinea pigs. These animals remained well and were normal at the end of fourteen days (fig. 2).

Presence of Acidophilic Cytoplasmic Inclusion Bodies in Rabbit Eyes Manifesting Keratoconjunctivitis: After the peak of the inflammatory reaction, which occurred about seventy-two hours after inoculation of the scarified cornea of

TABLE 1.—*Results of Animal Inoculation with Vesicular Fluid from Skin of a Patient with Erythema Multiforme Exudativum, Bullous Type*


Fluid Obtained on Third Day of Illness
Rabbit 1: Scarified cornea inoculated; keratoconjunctivitis, 3+
Eye washings
Rabbit 2: Scarified cornea inoculated; keratoconjunctivitis, 3+ rabbit killed for sections of cornea; acidophilic cytoplasmic inclusion bodies present
Eye washings
Five mice inoculated intracranially:
14N,* 14N, 14N, 14N, 2D
Fluid Obtained on Fourth Day of Illness
Rabbit 3: Scarified cornea inoculated; keratoconjunctivitis, 3+; bled for antibodies (table 2)
5 mice inoculated intracranially; all normal at fourteen days
Five mice inoculated intracranially
2K, 2D,† 14N, 14N
Two pooled brains
5 mice inoculated intracranially; all normal at fourteen days
2 guinea pigs inoculated intracranially; all normal at fourteen days

*Each number indicates the day a mouse was killed or found dead. All killed after fourteen days had no symptoms of disease.

†Animal found dead in forty-eight hours; brain unfit for passage.

rabbit 2 with the vesicular fluid obtained from the patient, the rabbit was killed and the eye removed for histologic study. The rabbit cornea manifesting the keratoconjunctivitis revealed evidence of an inflammatory process confined par-

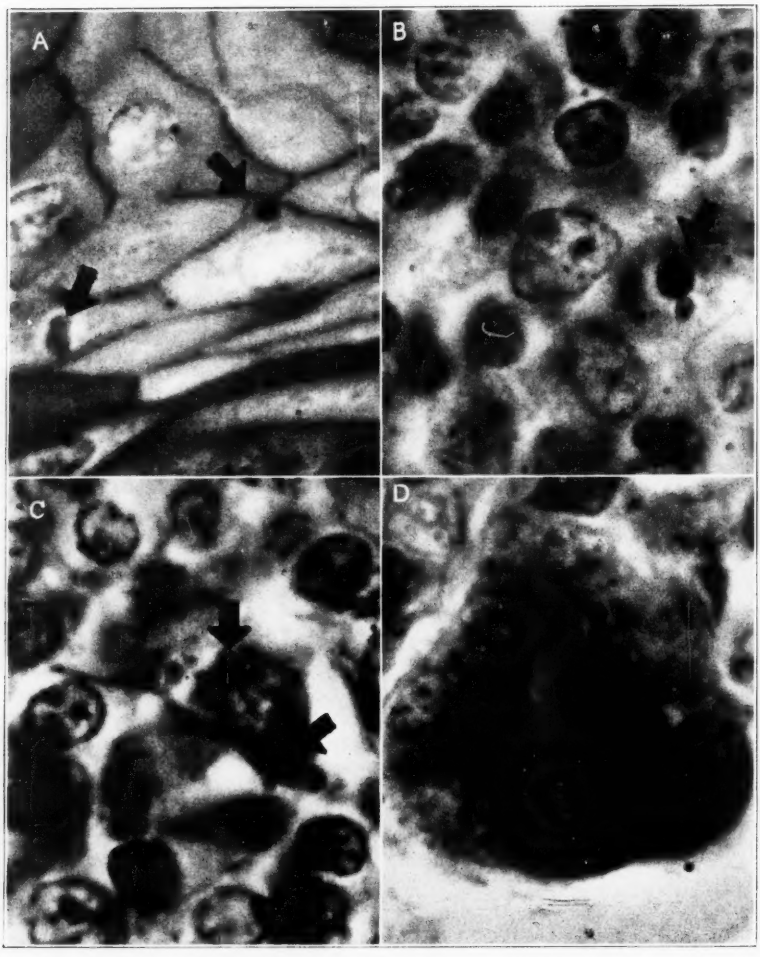


Fig. 2.—*A*, epithelial cells from cornea of rabbit with keratoconjunctivitis, showing acidophilic cytoplasmic inclusion bodies; *B* and *C*, inclusion bodies in mononuclear cells at junction of cornea and bulbar conjunctiva; *D*, large macrophage, containing numerous inclusion bodies. Oil immersion lens.

ticularly to the junction of the cornea with the ocular conjunctiva (fig. 2). Here, there was a rather extensive mononuclear cell infiltration. Only an oc-

casional polymorphonuclear cell could be seen. Bacteria were not seen in the inflammatory area. Acidophilic cytoplasmic inclusion bodies were observed in the proliferating, superficial corneal epithelium (fig. 2*A*), in the mononuclear cells infiltrating the limbus of the cornea and in the large mononuclear phagocytic cells observed in the deeper areas of the lamellar structure of the cornea. These bodies stained homogeneously a bright red (the color differing from that of the red blood cells or of the chromatin of the cells) with the Goodpasture (phenol-aniline-fuchsin) stain and varied from 3 to 6 microns in diameter. In most instances only one inclusion body could be seen in a cell. Occasionally a halo around the inclusion body could be observed. These acidophilic cytoplasmic inclusion bodies were observed only in sections stained with the Goodpasture stain and were not seen in any of the sectioned stained with hematoxylin eosin.

Neutralization with Rabbit Serum Against Virus of Herpes Simplex (HF Strain): Rabbit 1, in which a severe keratoconjunctivitis developed after inoculation with the vesicular fluid, was bled when in good health, on the thirteenth day after inoculation. This blood was then analyzed for the possible presence of a protective antibody against the virus of herpes simplex (HF strain). Various

TABLE 2.—*Results of Neutralization Tests Against Virus of Herpes Simplex with Serum of Rabbit Recovering from Keratoconjunctivitis*

Source of Serum and Virus	Dilutions of Virus*		
	10:2	10:3	10:4
Rabbit 1	3, 3, 4	3, 4, 4	6, 6, 6
Virus only	3, 3, 3	3, 3, 4	4, 4, 4

*Each number indicates the day on which a mouse died after cerebral inoculation with virus or serum-virus mixture in the various dilutions. A 1:2 dilution of rabbit serum was mixed with dilution of the virus of equal concentration.

dilutions of the virus (1:50, 1:500 and 1:5,000) were mixed with equal volumes of rabbit serum. The final dilutions of the virus, after being mixed with the rabbit serum, were $10,^{-2}$ $10,^{-3}$ and $10.^{-4}$ The serum-virus mixture was incubated for one hour in a refrigerator at 4 C. and then injected intracerebrally into young Swiss mice. The results of this neutralization test of the convalescent rabbit serum against the HF strain are presented in table 2.

These results indicate that there was no protective antibody in the convalescent rabbit serum against a virulent strain of the virus of herpes simplex. Unfortunately, determination of neutralization antibodies against the virus of herpes febrilis in the serum of the patient during convalescence was not made.

COMMENT

The review of the literature offers some evidence that the bullous type of erythema multiforme exudativum may be of an infectious nature. The herpetic nature of the disease, as described by Penny in 1899; the epidemics reported by Rigler in 1852,[9] by Duhring[10] in 1896,

by Guy[11] in 1918 and by Leipner[12] in 1935, and the failure of all workers to find a common bacteriologic agent also suggest that a virus may be the etiologic agent. However, as noted previously, Baader, Koke, Edgar and Syverton, and Ebert all failed to find a viral agent.

While a specific virus was not isolated from this patient, certain of the observations offer evidence that a virus was the etiologic agent in this case. The presence of herpetic lesions on the lip of the father preceding the illness in this patient is of interest, as is the presence of herpetic vesicular lesions in the mouth of the patient two days before the occurrence of the generalized eruption of the skin. The production of a severe keratoconjunctivitis in the rabbit eye, which could be transmitted in sterile washings to a second rabbit, suggests that a viral agent was present in the vesicular fluid and in the washings from the eye. Finally, the presence of acidophilic cytoplasmic inclusion bodies in the epithelial cells and the monocytic cells infiltrating the limbus of the scarified rabbit cornea inoculated with vesicular fluid is further evidence supporting the presence of a viral agent in the vesicular fluid. The failure of the agent in the bacteriologically sterile vesicular fluid to produce fatal encephalitis in the young Swiss mouse is evidence that this agent was likely not the virus of herpes simplex. The failure of antibodies to develop against the virus of herpes simplex (HF strain) in the rabbit convalescing from the keratoconjunctivitis is also against the possibility that this agent is the virus of herpes simplex. Finally, the virus of herpes simplex produces intranuclear acidophilic inclusion bodies while those observed in the cornea of the rabbit with keratoconjunctivitis were all cytoplasmic acidophilic inclusion bodies.

Several viruses have been isolated by other workers from vesicular lesions in the mouth similar to the lesions in this patient. Black,[16] and Dodd, Johnston and Buddingh,[17] in 1938, isolated a virus from the vesicular fluid of patients with aphthous stomatitis; in all probability, this virus is closely related to that of herpes simplex. Burnet and Lush[18] and

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16. Black, W. C.: Acute Infectious Gingivostomatitis ("Vincent's Stomatitis"), Am. J. Dis. Child. **56**:126 (July) 1938.

17. Dodd, K.; Johnston, L. M., and Buddingh, G. J.: Herpetic Stomatitis, J. Pediat. **12**:95 (Jan.) 1938.

18. Burnet, F. M., and Lush, D.: J. Path. & Bact. **42**:469, 1936; Inactivation of Herpes Virus by Immune Sera: Experiments Using Chorio-Allantoic Membrane Technique, J. Path. & Bact. **48**:275 (March) 1939.

Scott and Steigman[19] left little doubt that the agent of herpetic stomatitis is due to a virus of herpes simplex. They, however, found intranuclear inclusion bodies in both epithelial and neural cells. More recently, Buddingh and Dodd[20] have isolated an agent from the vesicular fluid and from the filtered stools, respectively, of infants with stomatitis and diarrhea. This agent produced a keratoconjunctivitis in rabbit eyes. The cellular infiltration observed, however, was polymorphonuclear, with considerable necrosis in the substantia propria of the cornea. In their work, intranuclear or cytoplasmic inclusion bodies were observed neither with the hematoxylin and eosin stain nor with Goodpasture's (phenol-anilin-fuchsin) method. This agent, however, produced no neutralization antibodies against the virus of simple herpes in convalescent patients.

In 1942, Adams and associates[21] reported the presence of acidophilic cytoplasmic inclusion bodies in the bronchial epithelial cells of infants who died of an atypical form of pneumonitis. These bodies varied from 3 to 6 microns in diameter and were similar to those reported in this paper.

SUMMARY

1. An agent capable of producing keratoconjunctivitis on the scarified rabbit cornea was isolated from the vesicular fluid obtained from a patient with erythema multiforme exudativum, bullous type.

2. Cytoplasmic inclusion bodies were observed in the epithelial and exudative cells of the rabbit cornea with keratoconjunctivitis.

3. The serum of a rabbit recovered from the keratoconjunctivitis failed to contain neutralizing antibodies against the virus of herpes simplex (HF strain).

These observations lend support to the previous suggestions in the literature that the causative agent of erythema multiforme exudativum, bullous type, is possibly of a viral nature.

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19. Scott, T. F. M.; Steigman, A. J., and Convey, J. H.: Acute Infectious Gingivostomatitis: Etiology, Epidemiology and Clinical Picture of Common Disorder Caused by Virus of Herpes Simplex, J.A.M.A. **117**:999 (Sept. 20) 1941.

20. Buddingh, G. J., and Dodd, K.: Stomatitis and Diarrhea of Infants Caused by Hitherto Unrecognized Virus, J. Pediat. **25**:105 (Aug.) 1944.

21. Adams, J. M.; Green, R. G.; Evans, C. A., and Beach, N.: Primary Virus Pneumonitis: Comparative Study of Two Epidemics, J. Pediat. **20**:405 (April) 1942.

NOTE.—Since the submission of this article for publication, 2 cases have been reported in which a significant rising complement fixation antibody titer was demonstrated in the blood against the psittacosis virus.[22]

22. Finland, M.; Jolliffe, L. S., and Parker, F., Jr.: Pneumonia and Erythema Multiforme Exudativum, Am. J. Med. 4:473 (April) 1948.

ANAPLASTIC EPITHELIOMA

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ALTHOUGH highly malignant, anaplastic epithelioma has received little attention from members of the medical profession and references to it in the literature are rather meager. Paget's tumor, Bowen's tumor (precancerous dermatosis) and nevocarcinoma (malignant melanoma) have been discussed in detail, but only as individual types of carcinoma, and not as parts of a general process. It is the purpose of this communication to present an organized description and classification of anaplastic epithelioma which we believe is distinct from epithelioma of the basal cell, spinobasal cell and prickle cell types.

CLASSIFICATION AND PATHOGENESIS

The cells in this type of malignant neoplasm are described as anaplastic, embryonic or undifferentiated. These terms are used interchangeably and characterize the cells only in part. A composite name embodying the features of all three would be preferable, since no one of these terms is entirely satisfactory. Epitheliomas characterized by this type of cell may be either primary, without preexisting lesions, or secondary to cancer or precancerous dermatosis (precancerosis). The present knowledge and concept of this subject should be enhanced by a classification of the various dermatologic entities which may eventuate in these two types of anaplastic epithelioma.

In the primary type, the process is not preceded by another dermatosis. Paget's tumor (fig. 1) and Bowen's tumor (fig. 2) represent the neoplastic states of Paget's disease of the nipple (fig. 3) and Bowen's disease (fig. 4), since an anaplastic epithelioma develops when the in-

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Types of Anaplastic Epithelioma and Dermatologic Entities Which May Eventuate in Them

GROUP 1: Primary type
- Direct type
- Bowen's tumor
- Paget's tumor

GROUP 2: Secondary type
- Cancer
  - Basal cell epithelioma
  - Prickle cell epithelioma
- Precancerous dermatoses
  - Keratoses
    - Seborrheic keratosis
    - Seborrheic verruca
    - Senile keratosis (flat and papillose)
    - Senile verruca (acanthoma)
    - Keratoses of radiotermatitis
  - Leukoplakia (leukokeratosis)
  - Kraurosis of the vulva
  - Junction nevus (melanoma)

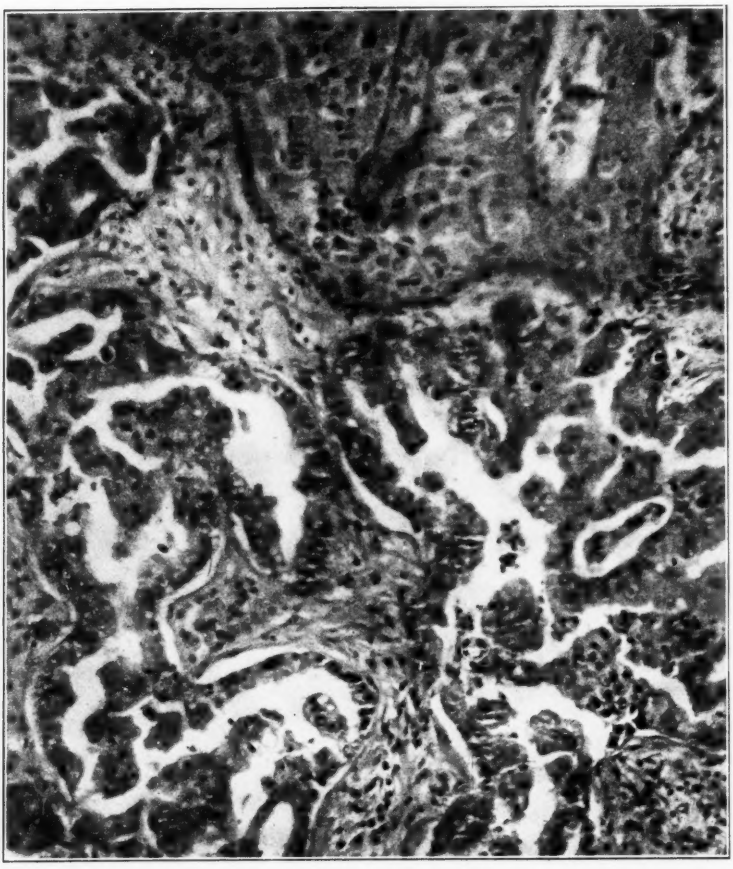

Fig. 1.—Paget's tumor, showing anaplastic cells in the epidermis as well as in the ducts; × 180.

volved epidermal cells proliferate and infiltrate the cutis. In both diseases, anaplastic change, not only of the basal cell zone but also of the epidermis above, may occur prior to invasion of the cutis. In the direct type of anaplastic epithelioma (fig. 5) the basal cell zone is the only part of the epidermis to undergo this change.

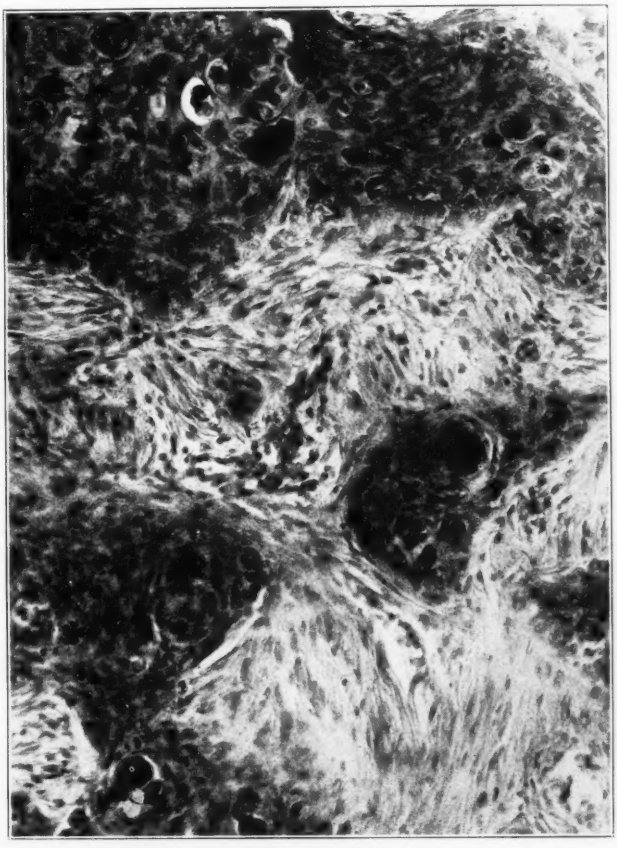

Fig. 2.—Bowen's tumor; × 160.

In the secondary type, anaplastic epithelioma develops from basal cell or prickle cell epithelioma (figs. 6 and 7) or from precancerous dermatoses.

Studies of our histologic sections lead us to believe that anaplastic epithelioma arising from a basal cell epithelioma usually originates, not

in the cells composing the mass of the epithelioma, but in the columnar basal cell layer marginating it. However, anaplastic epithelioma originating in a prickle cell epithelioma may arise either from the palisade layer or, when this is missing, from the cells of the original neoplasm. Anaplastic epithelioma arises more often from prickle cell epithelioma than from the basal cell epithelioma.

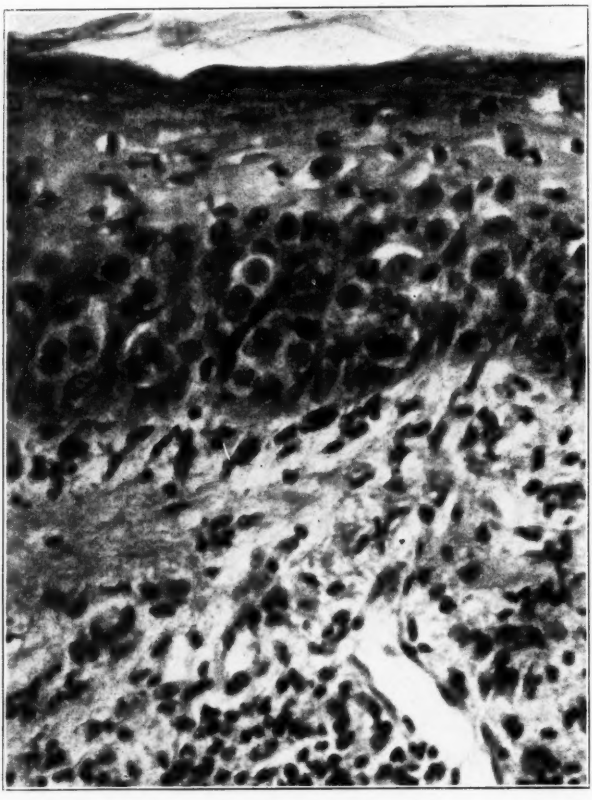

Fig. 3.—Paget's disease; × 409.

Anaplastic epithelioma may develop in seborrheic keratosis (fig. 8), seborrheic verruca, senile keratosis (both types), senile verruca (fig. 9) or in keratosis following radiation. The incidence in the seborrheic forms is less than in the senile keratoses. Precancerous conditions of the mucous membrane, such as leukoplakia, leukokeratosis and kraurosis of the vulva, may give rise to this variety of epithelioma. It is possible that mucous

membrane has a relatively higher incidence of this type of malignant growth than has skin. Junction nevus (melanoma) differs from the other types developing from precancerous dermatoses in that it can develop only into anaplastic epithelioma (figs. 10 and 11).

In our effort to formulate a classification of this type of epithelioma, we could find none that was beyond criticism. Although we did not in-

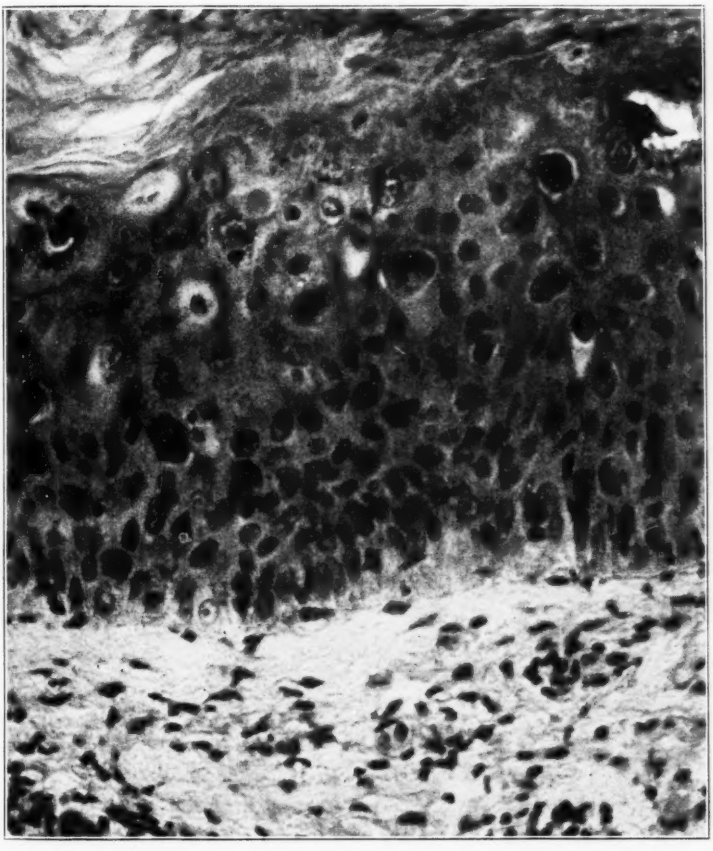

Fig. 4.—Bowen's disease; × 415.

clude them in our classification, we realize that spinobasal cell epithelioma and other preexisting lesions, such as arsenical keratosis, scars or lupus erythematosus, may also give rise to anaplastic epithelioma.

No attempt has been made to arrange the entities according to their potential degree of malignancy. In general, the intensity of malignant

change, as characterized by the appearance of the anaplastic or embryonal cell, is not the same in all the dermatoses considered. Furthermore, individual lesions of the same entity may show differences in the degree of malignancy.

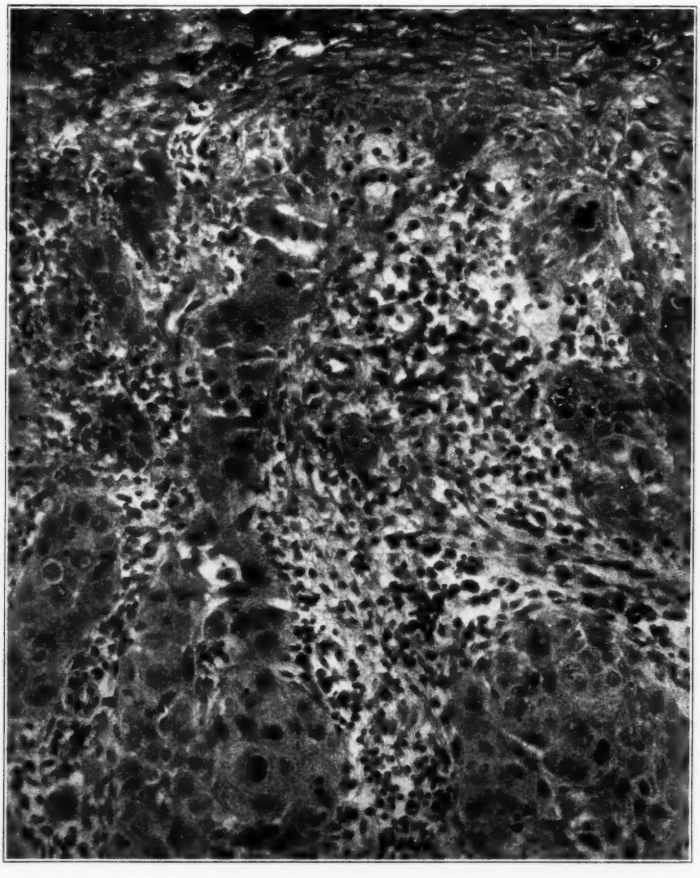

Fig. 5.—Anaplastic epithelioma arising direct from the mucous membrane; × 210.

As a rule, the least malignant are Bowen's tumor and the anaplastic epithelioma arising from basal cell epithelioma; the most malignant are nevocarcinoma and Paget's tumor, and the other diseases range between these types. As mentioned, this consideration is of value only in the interpretation of the over-all picture and does not apply necessarily to

specific cases. But, whether primary or secondary, whether arising from cancer or precancerous dermatosis, anaplastic epithelioma is relatively more malignant than other types of epithelioma and lesions in which the cells are equally undifferentiated, or anaplastic, are of equal malignancy.

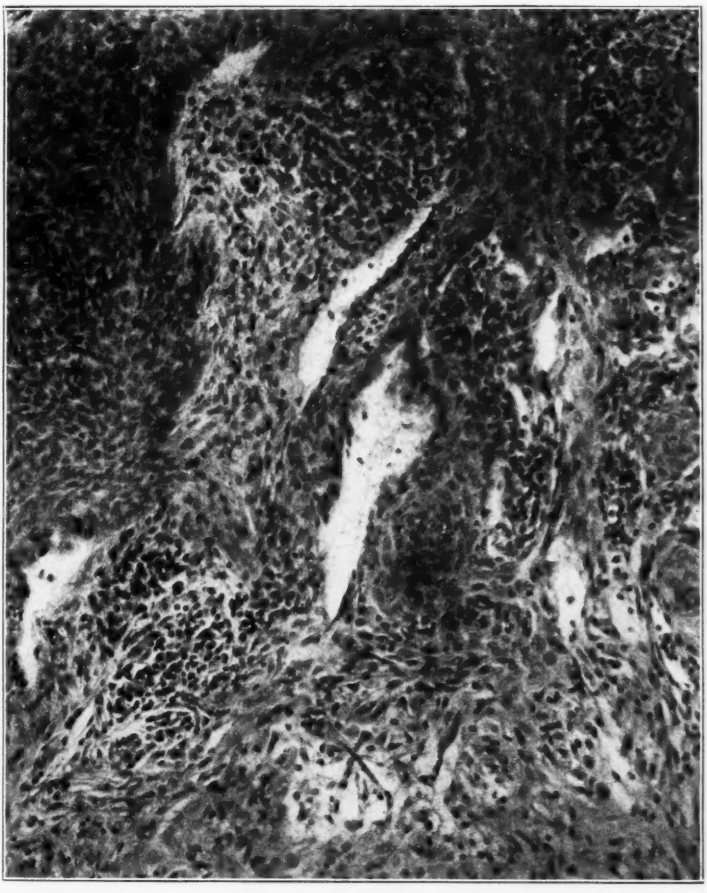

Fig. 6.—Anaplastic epithelioma arising from a basal cell epithelioma; × 180.

CLINICAL DIAGNOSIS

There is so little mention of anaplastic epithelioma that one must assume that it frequently goes unrecognized and that, therefore, the diagnosis is seldom made. Other types, particularly prickle cell epithelioma, are more often suggested.

When the lesion is of the primary type, such as Bowen's or Paget's tumor, the clinical diagnosis of anaplastic epithelioma may be fairly easy. However, it is extremely difficult, and usually impossible, to identify this form of malignant growth when it develops directly from the epidermis or secondarily from a precancerous dermatosis or from cancer. Certain

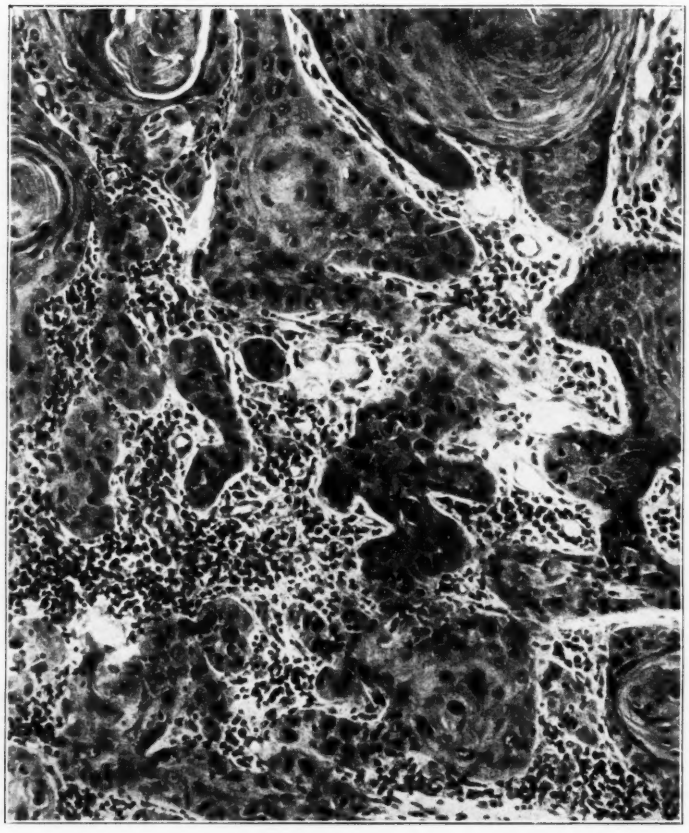

Fig. 7.—Anaplastic epithelioma arising from a prickle cell epithelioma; × 164.5.

clinical features may be suggestive. A sudden increase in growth in a nonmalignant lesion, more intense and rapid than is usual with other types of carcinoma, or the appearance of such a change in a lesion known to be malignant would indicate the presence of an anaplastic epithelioma. This is particularly true if the lesion has been subjected to undue trauma

or inadequate therapy, whether it be local administration of escharotics, surgical intervention or irradiation.

The appearance of an anaplastic epithelioma in a junction nevus offers comparatively little diagnostic difficulty. A nevocarcinoma can develop only from a junction nevus, and a junction nevus can give rise only to a nevocarcinoma. Thus, junction nevus is the only precancerous

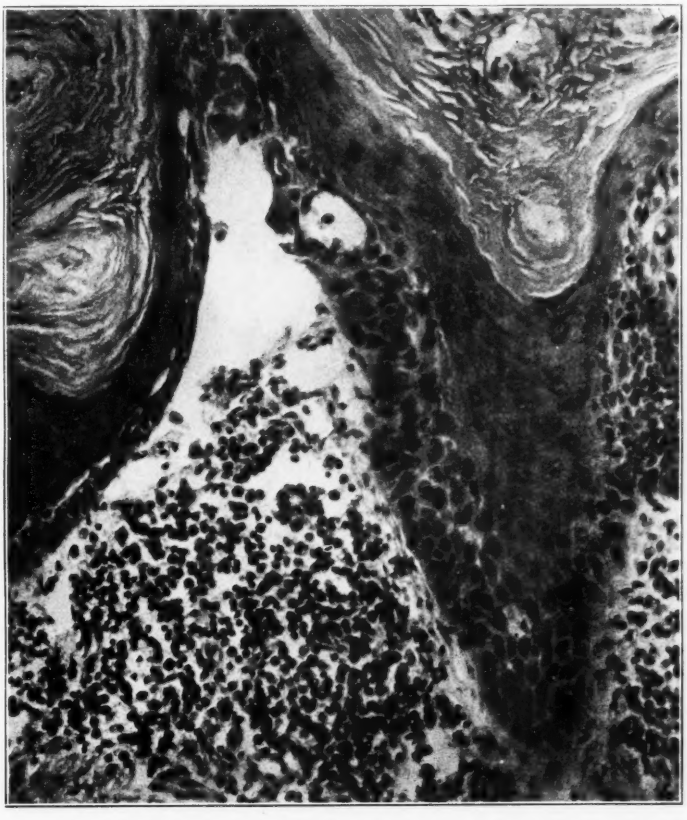

Fig. 8.—Anaplastic epithelioma arising from seborrheic keratosis; × 253.

dermatosis in which the type of epithelial neoplasm that will ensue in the event of a malignant change is predetermined. This fact facilitates the clinical diagnosis of early nevocarcinoma; late nevocarcinoma is usually not a diagnostic problem.[1]

1. Sachs, W.; MacKee, G. M.; Schwartz, O. D., and Pierson, H. S.: Nevocarcinoma, J. A. M. A. **135**:216 (Sept. 27) 1947.

Except for Bowen's tumor, Paget's tumor and nevocarcinoma, the clinical diagnosis of anaplastic epithelioma is difficult and infrequently entertained. The presence of a neoplasm of highly malignant behavior should suggest the possibility of this type of epithelioma. Practically, however, the existence of an anaplastic epithelioma is determined in most instances by microscopic study.

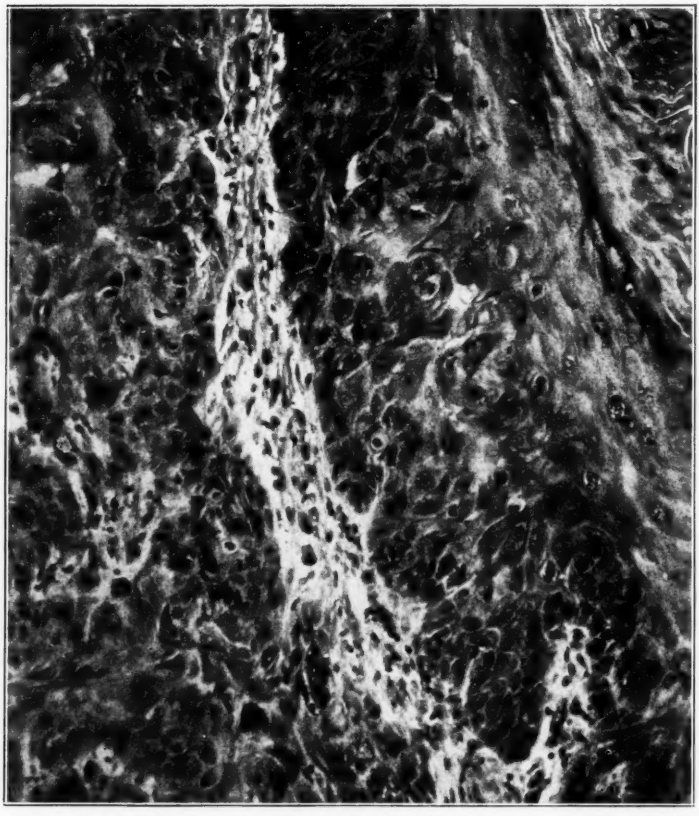

Fig. 9.—Anaplastic epithelioma arising from senile verruca; × 213.

MICROSCOPIC DIAGNOSIS

The microscopic diagnosis of anaplastic epithelioma depends on the presence of collections of anaplastic cells. The anaplastic cell is large, tends to be round and has a definite cell wall. The nucleus is also large, round and hyperchromatic. Multinucleated cells are frequent, and mitotic

figures may be demonstrated. The cytoplasm may appear granular, clear or homogeneous; the prickles are missing. It is evident that this cell differs from the parent cell in size, in staining characteristics and in its relation to surrounding cells. It should be emphasized that it is not a

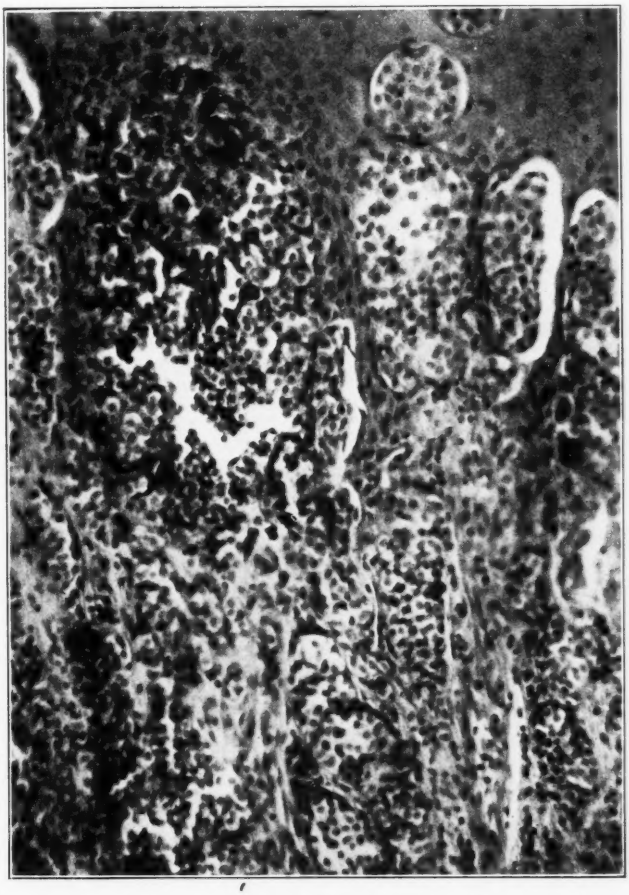

Fig. 10.—Early nevocarcinoma; × 180.

basal or a prickle cell, but one that possesses its own individual characteristics. These cells may be arranged in various-sized masses, but small groups and isolated cells are frequently seen.

A margin of regular columnar basal cells or a palisade layer may or may not be seen about any epithelial malignant growth, whether infil-

trating or not, and its presence or absence categorizes it as intraepidermal or extraepidermal. This is of great importance in determining the degree of malignancy, the possibility of metastasis and the prognosis. This confining layer of basal cells is at least partly, and usually entirely, absent in anaplastic epithelioma. When a palisade layer is present about a malig-

Fig. 11.—Late nevocarcinoma; × 180.

nant epithelioma, it is usually lost in the transition to the anaplastic type. However, anaplastic change, preceding infiltration, may occur while the columnar layer is partially or wholly present. The presence of this margin in early cases of Bowen's disease depends on whether or not the process started in the basal cell zone of the epidermis. Paget's disease usually be-

gins in this layer. Thus, the margin of columnar basal cells may be observed more often in Bowen's than in Paget's disease.

As in other cancerous and precancerous dermatoses, a cellular reaction, or inflammatory-protective zone, is seen about anaplastic epithelioma. However, this reaction tends to be less intense and is characteristic of a highly malignant type of neoplasm; i.e., it is composed of simple cells (small round cells and wandering connective tissue cells), in contrast to fibrosis or plasma cells. At times, as in highly malignant anaplastic epitheliomas, there may be scant or no cellular infiltration about the neoplasm.

Once the diagnosis of anaplastic epithelioma is established, it is necessary to decide which type is present. The differentiation of one type from another may prove difficult or impossible if study is confined to a restricted microscopic field or to cytologic study of the anaplastic area. The primary types may be differentiated only by study of the entire section and by interpretation of the concomitant features, i.e., configuration, pigment, presence of ducts and appearance of the epidermis. The differentiation of the secondary forms of anaplastic epithelioma depends on the detective ability of the examiner and on the characteristic microscopic picture of the original dermatosis.

COMMENT

The anaplastic cell results from changes in a preexisting epithelial cell and is the end product of anaplasia, the retarded or malignant form of dyskeratosis. The term was first used by von Hansemann,[2] who defined it as an alteration in the cell, not easily recognizable by its form, but consisting in changed histologic characteristics which allow it to proliferate rather than to function normally. He stated the belief that the irregular and abnormal mitosis of tumor cells was an indication of the production of races of cells possessing greater capacity for multiplication. This propagation of similar abnormal cells is a malignant characteristic, encountered in anaplastic epithelioma and, in a milder form, in prickle cell epithelioma.

The popular concept is that this change is in the nature of a reversion toward an embryonic cell. The theory that it results from an arrest in development of embryonic cells has been propounded. We suggest that this change may, rather, be an abnormal progression, resulting in the development of a cell with the highest malignant properties. With such malde-

2. Von Hansemann, D. P.: Studien über die Spezificität, den Altruismus und die Anaplasie der Zellen, mit besonderer Berücksichtigung der Geschwülste, Berlin, A. Hirschwald, 1893; Die mikroskopische Diagnose der bösartigen Geschwülste, ibid., 1897.

velopment, little of the normal function of the cell is retained, contrary to the behavior of an embryonic cell.

Malignant change developing in basal cells, with or without neoplastic proliferation, may take place in different ways. The usual picture is that of the ordinary basal cell epithelioma in which, instead of forming prickle cells, the basal cells proliferate as basal cells. In view of such abnormal behavior of the cell, it seems unlikely that these daughter cells can produce prickle cells; and, since the neoplasm thus formed is composed for the most part of normal-appearing cells, it is often of lowest grade malignancy. On the other hand, a fully developed anaplastic cell may form directly from a basal cell without any intermediary stage. This malignant change may be observed in the basal cells of the epidermis before proliferation takes place, as in Bowen's or Paget's disease, or in the basal cells marginating a basal cell epithelioma. We rarely have seen this change in the cells within the basal cell tumors.

Once the normal prickle cell has differentiated from the basal cell, it may undergo anaplasia and form a prickle cell epithelioma, which may, in turn, remain as such or become an anaplastic epithelioma. The cells of a prickle cell epithelioma differ from those of an anaplastic epithelioma in that they retain their prickles and, while showing changes similar to those of anaplastic cells, do so to a lesser degree. In other words, they show the changes of anaplasia but do not attain the final characteristics of the anaplastic cell. In contrast to basal cell epithelioma, any of the active cells of a prickle cell epithelioma may give rise to an anaplastic epithelioma. As previously stated, if a palisade layer is present about the prickle cell epithelioma, these marginating cells may become anaplastic. We wish to emphasize that the foregoing discussion is theoretic.

SUMMARY

We consider anaplastic epithelioma a distinct type of cancer and have endeavored to describe and classify it. We believe that it may be either primary or secondary to cancer or precancerous dermatoses. In the discussion of this form of cancer we suggest that anaplasia may be, not a reversion toward the embryonic state, but an abnormal development. In the past, the diagnosis of anaplastic epithelioma was seldom made, this type of tumor often being considered either basal cell or prickle cell epithelioma, grade 3 or grade 4 (Broders' index).

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TREATMENT OF EARLY SYPHILIS WITH SMALL DOSES OF CRUDE PENICILLIN

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AND
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SOON AFTER penicillin was found to be effective in the treatment of early syphilis,[1] the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council, assigned to the department of dermatology and syphilology at the University Hospitals and the Cleveland City Hospital the treatment of early infectious syphilis with three schedules, utilizing small amounts of penicillin (1,000 and 1,500 units) alone or in combination with oxophenarsine (mapharsen^{R}). Between November 1943 and June 1944, 159 patients with syphilis exhibiting dark field—positive primary or secondary lesions were treated by one of these three schedules. An immediate favorable effect on disappearance of the mucocutaneous lesions and reversal of the serologic titer was noted; however, after a few months' observation the rate of relapse was so high that these schedules were abandoned. A report on the observation of these patients was make by Binkley and Kile[2] in March 1945, after the patients had been followed from six to ten months. Continued observation on these patients has been maintained for thirty-four months or longer, and it is the purpose of this paper to report the subsequent data which have been obtained.

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research Development and Western Reserve University, and under a grant in aid from the National Institute of Health, United States Public Health Service.

1. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis, Am. J. Pub. Health **33**:1387 (Dec.) 1943.

2. Binkley, G. W., and Kile, R. L.: Rapid Treatment of Early Syphilis with Small Dosages of Penicillin: Observations in One Hundred and Fifty-Nine Cases, Arch. Dermat. & Syph. **51**:200 (March) 1945.

MATERIAL AND METHOD

GROUP 1.—Between November 1943 and January 1944, 31 patients with early infectious syphilis were treated with 1,000 Oxford units of crude aqueous sodium penicillin administered intramuscularly every three hours for a total of

TABLE 1.—*Data on Three Schedules of Penicillin Therapy*

Total Dose	60,000 Units	60,000 Units Plus 320 Mg. Mapharsen® (40 Mg. Daily for 8 Days)	300,000 Units
Total no. of patients	31	47	81
Sex and race			
M White	1	3	9
M Negro	11	23	36
F White	2	2	5
F Negro	17	19	31
Herxheimer reactions	26 (84%)	38 (80.8%)	61 (75.3%)
Patients lapsed from observation			
Number	9	12	28
Per cent	27.6	26	34.5
Seroresistant patients	2	0	8
Serologic relapses only	4	3	9
Seroclinical relapses	9	16	15
Neurologic recurrences	1	0	3
Relapses			
0—6 mo.	12	13	12
Over 6 mo.	4	6	23
Patients seronegative and clinically well	6	15	18
Pregnant patients treated	3	1	2
Nonsyphilitic infant delivered	3	1	1
Syphilitic infant delivered	0	0	1

sixty injections. One patient had seronegative primary syphilis; 5 patients had seropositive primary syphilis, and the remaining 25 patients had secondary syphilis. Two of these patients were retreated because the schedule of therapy was considered inadequate, although both patients were seronegative and clinically well when retreated and remained so during the subsequent follow-up observation. In 3 of the patients with secondary syphilis, pregnancy was a complication at the time of treatment. The complete data are fully presented in table 1.

GROUP 2.—Between December 1943 and February 1944, 47 patients with early infectious syphilis were treated with a similar dose of crude aqueous sodium

penicillin, and concomitantly 40 mg. of oxophenarsine hydrochloride was administered daily by the intravenous route for a total of 320 mg. These 47 patients included 8 with seronegative primary syphilitic infections, 11 patients with seropositive primary syphilitic infections and 28 patients with secondary syphilis. In 1 of the patients with secondary syphilis pregnancy was a complication at the time of treatment. The complete data are shown in table 1.

GROUP 3.—Between March 1944 and June 1944, 81 patients with early infectious syphilis were treated with 5,000 units of crude aqueous sodium penicillin administered every three hours intramuscularly, for a total of sixty injections, or 300,000 units. The complete data are shown in table 1. Of these 81 patients, 6 had seronegative primary syphilitic infections; 18, seropositive primary syphilitic infections, and 57, secondary syphilis. In 2 of the patients with secondary syphilis pregnancy was a complication at the time of treatment.

RESULTS OF TREATMENT

Patients Who Had Relapses.—GROUP 1.—Of the 31 patients treated with a total of 60,000 units of penicillin, 16, or 72.7 per cent, were considered to have had relapse. Three patients with seropositive primary syphilis and 13 with secondary syphilis had a relapse. The latter group included 3 patients with secondary syphilis complicating pregnancy, all of whom had relapses; however, the babies were born alive at term, and the subsequent observation of these children for from eleven to thirty-eight months revealed no evidence of syphilis, either clinical or serologic. Twelve of the patients had a relapse within the first six months after treatment. Three patients had a relapse within the second six months after treatment; this number included 2 patients who were seroresistant. Only 1 patient had a relapse within the third six months of the observation period.

GROUP 2.—Of the 46 patients treated with a total of 60,000 units of penicillin and, concomitantly, oxophenarsine hydrochloride (mapharsen^{R}), 19, or 55.9 per cent, were considered to have had relapses. These 19 patients included 2 with seronegative primary syphilitic infections, 3 with seropositive primary syphilitic infections and 14 with secondary syphilis. Thirteen of the patients had a relapse within the first six months; the remaining 6 had a relapse within the second six months.

GROUP 3.—Of the 81 patients treated with a total of 300,000 units of penicillin, 35, or 66 per cent, were considered to have had relapses. These relapses occurred in 6 patients with seropositive primary syphilitic infections and in 29 patients with secondary syphilis. One of the 2 patients with secondary syphilis complicating pregnancy had a relapse. The baby was born alive with a positive serologic reaction and subsequently was found to have congenital syphilis, which was successfully treated. Twelve of the patients had relapses within the first six months; 20 patients, within the second six months, and 3 patients, within the next

twelve months. In no case could reinfection be proved, although it was suspected in several instances.

Patients Who Were Serologically and Clinically Well.—Group 1.—Six patients of the group of 31, or 27.3 per cent, who were treated with the smaller amount of penicillin alone were clinically and serologically well for the duration of their post-treatment observation period. One patient had seronegative primary syphilis; 2, seropositive primary syphilis, and 3, secondary syphilis. All the patients in this classification reached seronegativity by the sixth month or before. Only 1 patient was observed for less than twelve months; the remaining patients were observed from twelve to twenty-four months.

Group 2.—Fifteen patients of this group, or 44.1 per cent, were clinically and serologically well for the duration of their post-treatment observation period. Four had seronegative primary syphilis; 4, seropositive primary syphilis, and 7, secondary syphilis. Of the 7 patients with secondary syphilis, 1 had syphilis complicating pregnancy. This patient had been four months pregnant when treated, became serologically negative two months after treatment and remained so for the ensuing fifteen months, up to the time of her last visit. A normal boy was delivered who was still serologically negative and clinically well at end of thirty-one months of observation.

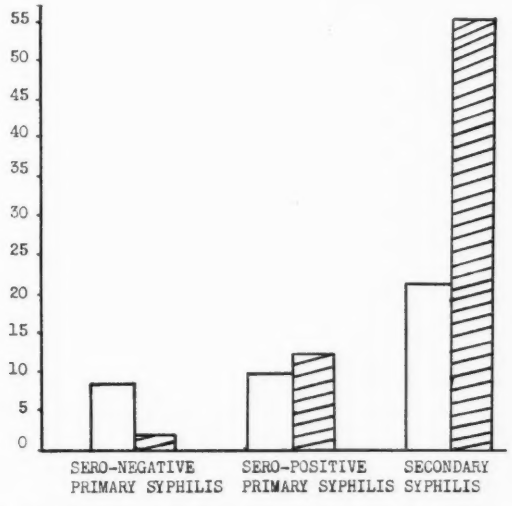
All the patients in this classification reached seronegativity by the fifth month of observation or before. Three patients were observed for less than twelve months; 3, for less than eighteen months; 4, for less than twenty-four months, and 5, for more than twenty-four months.

Group 3.—Eighteen patients of the group of 81, or 34 per cent, who were treated under this schedule were clinically and serologically well for the duration of their post-treatment observation period. Three of these patients had seronegative primary syphilis; 4, seropositive primary syphilis, and 11, secondary syphilis. Of the last group, 1 patient had secondary syphilis complicating pregnancy. Both the mother and the child remained serologically and clinically well for an observation period of over two years. All the patients in this classification reached seronegativity by the eighth month or before. Six patients were observed for less than twelve months after treatment; 4, from eighteen to twenty-four months, and 8, for more than twenty-four months.

COMMENT

In an observation period of thirty-four months or longer on 109 of 159 patients with early syphilis treated with small amounts of penicillin alone or combined with mapharsen,[R] certain interesting points were brought to light (tables 1 and 2).

The rate of relapse and the incidence of the patients who were serologically and clinically well were approximately the same whether 60,000 or 300,000 units of penicillin was utilized in the treatment schedule. The only difference noted was that the rate of relapse appeared to be pro-



Accumulative results for patients treated with one of three schedules using small doses of crude penicillin. The rectangles representing cures are clear; those representing relapses are cross hatched.

TABLE 2.—*Results of Three Therapeutic Schedules Using Small Amounts of Crude Penicillin*

Schedule	No. of Patients	Seronegative Primary Syphilis			Seropositive Primary Syphilis			Secondary Syphilis		
		No. Treated	Relapses	Cures	No. Treated	Relapses	Cures	No. Treated	Relapses	Cures
60,000 units	22	1	0	1	5	3	2	16	13	3
60,000 units plus mapharsen[R]	34	6	2	4	7	3	4	21	14	7
300,000 units	53	3	0	3	10	6	4	40	29	11
Total	109	10	2	8	22	12	10	77	56	21
Per cent			20	80		54.6	45.4		72.7	27.3

longed by the larger amount of penicillin administered. Arsenic in the form of oxophenarsine hydrochloride (mapharsen[R]) administered concomitantly with the penicillin was perhaps an additional curative factor.

Small amounts of penicillin given during pregnancy, even though they were insufficient to cure the mother, had the decidedly beneficial effect of either protecting the baby or rendering it serologically negative and clinically well over a long post-treatment period of observation.

In cases of early infectious syphilis, even with the use of small amounts of penicillin, the serologic reaction has a tendency to reverse to negativity early and rapidly if the patient is going to get well.

The three treatment schedules made use of a commercial sodium penicillin that was of a relatively crude nature, containing the forms G, X and F and a very small amount of K, in addition to other, unknown substances. It has been indicated by Dunham and Rake[3] and others in animal and in vitro experimentation that this crude penicillin has spirocheticidal properties that may be due in part to extraneous components of the drug. The data shown in this paper would rather substantiate this view. It is difficult to believe that the unitage of penicillin used in these studies would have been sufficient to produce a cure in such a large number of cases of early syphilis without some other curative factor being involved. Table 2 and the chart reveal a significant difference in the percentage of cures, depending on the stage of syphilis at which treatment was started and on the schedule used.

SUMMARY

We report the results of continuous observation for a period of thirty-four months or longer on a total of 109 of 159 patients with dark field—positive early syphilis who were treated by one of three intensive schedules, all utilizing crude sodium penicillin administered in divided doses. In one schedule, in addition to the crude penicillin, oxophenarsine hydrochloride (mapharsen[R]) was given in divided daily doses of 40 mg., for a total of 320 mg. In two schedules the penicillin was administered in doses of 1,000 units every three hours for a total of 60,000 units, while in the third schedule, 5,000 units was administered every three hours for a total of 300,000 units.

Of 109 patients observed up to date, 80 per cent with seronegative primary syphilis, 45 per cent with seropositive primary syphilis and 27 per cent with secondary syphilis were "cured." Moreover, of the 6 patients

3. Dunham, W. B., and Rake, G. O.: The Relative Activity of Partially Purified Penicillin and of Crystallin Penicillin G on Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **29**:214 (March) 1945.

with syphilis complicating pregnancy although only small doses of crude penicillin were administered, 5 children observed over a long period were found to be free from the disease.

It is suggested that these data indicate that with the low dosage, low unitage penicillin therapy employed there may have been spirocheticidal components other than the penicillin in the crude mixture.

It is not intended from the results of this study to advocate penicillin in such a dosage for the treatment of syphilis.

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KERATOSIS BLENNORRHAGICA

Response to Streptomycin; Report of a Case

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IN THE half-century which has elapsed since the original description of keratosis blennorrhagica by Vidal[1] in 1893, it has become generally agreed that this disease represents a distinct clinical entity. In 1942 Keim[2] analyzed the disease from an etiologic standpoint and described the fundamental histologic changes. Since that time numerous investigators have anvanced methods of treatment; these have in the main been directed against the general infection, local treatment proving to be of little value.

Among the therapeutic measures reported favorably are intravenous injections of 1 per cent solution of merbromin N. F., (mercurochrome^{R}), by Willmott[3] in 1926, and the use of autogenous vaccines, by Scholtz,[4] about one year later. Downing[5] reported rapid recovery in a patient following double vesiculectomy and prostatotomy. Sherman, Blumenthal and Heidenreich[6] stressed the importance of treating the primary focus and stated the opinion that local treatment of the arthritis and dermatitis was of only minor value.

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1. Vidal, E.: Nécrologie, Ann. de dermat. et syph. **4**:3, 1893.
2. Keim, H. L.: The Histogenesis of Keratoderma Blennorrhagicum, Arch. Dermat. & Syph. **9**:423-440 (April) 1924.
3. Willmott, C. B.: "Keratodermie blennorrhagique" (Vidal), Arch. Dermat. & Syph. **13**:17 (Jan.) 1926.
4. Scholtz, M.: A Syndrome of Blennorrhagic Keratoderma, Arch. Dermat. & Syph. **15**:165 (Feb.) 1927.
5. Downing, J. G.: Keratoderma Blennorrhagicum: Report of a Case, J. A. M. A. **102**:829 (March 17) 1934.
6. Sherman, W. L.; Blumenthal, F., and Heidenreich, J.: Blennorrhagic Balanitiform Keratoderma, Arch. Dermat. & Syph. **39**:422 (March) 1939.

Favorable response to fever artificially induced by various means has been reported by Willmott,[3] Epstein[7] and Epstein and Chambers.[8] In 1940 Combes, Dietrich and Cohen[9] reported 2 cases in which successful results were obtained with fever induced by means of the inductotherm and concluded that the method was superior to any which had previously been suggested.

Combes and Behrman[10] successfully treated a patient with keratoderma blennorrhagicum with massive doses of vitamin A and suggested that a deficiency in intake, absorption or conversion of this vitamin might be a basic factor in the appearance of the disease.

Use of the various sulfonamide drugs has been recommended, but results have been variable and inconsistent. Gateley[11] reported cure in an early case by internal administration of sulfathiazole and the application of 10 per cent silver nitrate to the local cutaneous lesions. Carr and Friedman,[12] in reporting a fatal case with autopsy, emphasized the "failure of sulfanilamide and sulfathiazole to alter appreciably the course of the disease, although administered in large doses during an arthrocutaneous relapse." They also called attention to the tendency of cutaneous lesions to appear after a series of treatments with artificial fever (with temperatures to 104 F.) for the arthritis. In 1945 Satulsky[13] reported the favorable response in a typical case of keratoderma blennorrhagicum to penicillin and sulfonamide drugs in massive doses. The value of this form of therapy was confirmed by Emmet.[14]

A search of the available literature revealed no record of the use of streptomycin in the treatment of keratoderma blennorrhagicum. In view

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7. Epstein, E.: Hyperpyrexia in the Treatment of Keratoderma Blennorrhagicum, Am. J. Syph., Gonor. & Ven. Dis. **21**:148 (March) 1937.

8. Epstein, E., and Chambers, S. O.: Keratosis Blennorrhagica with Corneal Lesions, Arch. Dermat. & Syph. **36**:1044 (Nov.) 1937.

9. Combes, F. C.; Dietrich, C., and Cohen, J.: Keratosis Blennorrhagica: A Brief Review and Report on the Effects of Hyperyrexia in Its Treatment, J. A. M. A. **114**:2078 (May 25) 1940.

10. Combes, F. C., and Behrman, H. T.: Use of Vitamin A in Keratosis Blennorrhagica: Successful Treatment with Massive Doses, Arch. Dermat. & Syph. **46**:728 (Nov.) 1942.

11. Gateley, J. R.: Case of Keratodermia Blennorrhagicum (Gonorrheal Dermatitis), U. S. Nav. M. Bull. **45**:1159 (Dec.) 1945.

12. Carr, J. L., and Friedman, M.: Keratodermia Blennorrhagicum: Report of a Case with Autopsy, Am. J. Path. **20**:709 (July) 1944.

13. Satulsky, E. M.: Keratoderma Blennorrhagicum: Brief Review and Report of a Case Treated with Penicillin, Am. J. Syph., Gonor. & Ven. Dis. **29**: 361 (May) 1945.

14. Emmet, R.: Keratosis Blennorrhagica: Its Response to Penicillin, Arch. Dermat. & Syph. **53**:278 (March) 1946.

of the reports of Miller and Bonhoff[15] that gonococci resistant to penicillin were susceptible to streptomycin in vitro and their conclusion that the mode of action of streptomycin on the gonococcus differs from that of penicillin, it seemed desirable to use streptomycin in a penicillin-resistant case of keratoderma blennorrhagicum. Consequently, a case was selected in which the disease had been present for seven months and had proved refractory to massive doses of sulfonamide drugs and penicillin. Streptomycin was administered by intramuscular injection, with cessation of all symptoms and clearing of cutaneous lesions.

REPORT OF CASE

History.—A Negro soldier aged 27, unmarried, was admitted to the hospital on April 3, 1947, complaining of a persistent urethral discharge and cutaneous lesions which involved the anterior aspect of the legs, the soles and palms and the nails of both hands and feet. These lesions had been present for three months. Neither the cutaneous lesions nor the urethritis had responded to penicillin and sulfonamide compounds which had been administered on an outpatient basis in very large doses.

The patient's past history revealed that he had gonorrhea in February 1946 and had been treated with penicillin, which caused the disappearance of the discharge after one month. Concurrently with the discharge, the patient had noted "crusting sores" on his legs and a thickening of his palms and soles. These cutaneous lesions diminished in size at the time the urethral discharge disappeared but did not clear completely for five months.

His present illness began in January 1947. While serving in Korea, the patient again contracted gonorrhea. Simultaneously with onset of the urethritis there appeared multiple crusting cutaneous lesions over the anterior aspects of both legs and thickening of the palms and soles. There was an associated elevation of the nails of both hands and feet, due to a yellowish, granular material. The patient was placed under treatment with intermittent short courses of penicillin, in a dosage of 50,000 units every three hours, with no improvement of the lesions. A total of 1,250,000 units of penicillin was administered over a period of two months. Concurrently with penicillin, the patient received large doses of sulfonamide drugs, without appreciable effect on the urethritis or the dermatitis. Urethral smears showed numerous gram-negative intracellular diplococci. A tentative diagnosis of keratoderma blennorrhagicum was made, and the patient was admitted to the hospital.

Physical Examination.—Examination on admission showed that the patient was well developed and fairly well nourished; he was ambulatory but complained of general malaise. His weight was 150 pounds (68 Kg.), which represented a loss of 10 pounds 4.5 Kg.) since the onset of his present illness. Physical examination revealed no abnormalities except in the skin and the genitourinary system.

The cutaneous lesions involved the legs, the soles and the palms and the nails of both hands and feet. Irregularly distributed over the anterior aspect of the legs were well defined plaques, from 0.5 to 4.5 cm. in diameter. They varied in shape and in two areas had coalesced to form large, coinlike lesions. The plaques were

15. Miller, C. P., and Bonhoff, M.: Streptomycin Resistance of Gonococci and Meningococci, J. A. M. A. **130**:485 (Feb. 23) 1946.

dirty, elevated about 3 mm. above the surface of the skin and covered with a yellowish, waxy scale, which could be removed with difficulty. On removal of the scale, a denuded surface was left, but no bleeding points were seen. A few lesions were definitely horny and conical. No vesiculation was noted, but several areas of pustulation were present. The most prominent feature was the lamellar crusts, which resembled rupia. The eruptions were painless on manipulation.

The lesions on the soles were generalized but most pronounced on the anterior part and the heel. These lesions closely resembled those on the legs except that they showed more keratosis. Many of these plaques had coalesced, making walking painful. Beneath the plates of all the nails of both hands and feet was seen a yellowish, waxy, honeycomb-like material, which could be removed with difficulty. This material raised the nails at their free borders, and the distal portions of the finger nails were brittle and broken. There was no evidence of arthritis.

There was a thin, purulent urethral discharge of moderate amount. The prostate was slightly enlarged, soft, boggy and tender. Phimosis was present, and when the foreskin was retracted a short distance, a dirty, undermined ulcer could be seen involving the cornal sulcus.

Laboratory Examinations.—Urethral smears showed gonococci. Repeated dark field examination of the penile lesion did not reveal Treponema pallidum, and Hemophilus ducreyi could not be demonstrated in repeated smears or on culture. The blood count was 4,800,000 erythrocytes, 13.8 Gm. of hemoglobin and 8,500 polymorphonuclear leukocytes, with 75 per cent polymorphonuclear leukocytes, 23 per cent lymphocytes and 2 per cent monocytes. The Wassermann reaction of the blood was consistently negative, and the corrected sedimentation rate was 36 mm. per hour. The Frei test gave a negative reaction; the Ito-Reenstierna reaction for chancroid was positive. Direct and cultural examinations of lesions of the nails revealed no evidence of fungous infection.

Course.—Immediately on his admission, repeated dark field examinations were made of the penile lesion, all of which failed to show T. pallidum. The reaction to the Kahn test was negative. Treatment was started with sufathiazole in doses of 1 Gm. every four hours. This therapy was continued from April 3 to 16, for a total of 84 Gm. On April 14 a urethral smear revealed numerous gram-negative intracellular diplococci. No improvement had been noted in the cutaneous lesions or in the urethral discharge. Beginning on April 17, penicillin was administered intramuscularly every three hours in doses of 50,000 units, for a total amount of 5,700,000 units. No improvement was noted in the cutaneous lesions or in the urethral discharge. A circumcision was performed, and sulfathiazole therapy was again instituted in doses of 1 Gm. every four hours, from June 13 to July 5, for a total of 138 Gm. On June 22 penicillin was used as a supplement in doses of 50,000 units every four hours for a total of 5,600,000 units. No improvement was evident, and the patient then had a more extensive ulceration in the scar of the circumcision. Repeated examinations of this lesion showed no Donovan bodies, and the dark field examination revealed no spirochetes. In view of the patient's poor response to sulfonamide drugs and penicillin, it was decided to administer streptomycin. Concurrently with the institution of streptomycin therapy, photographs shown in figure 1 were made. Biopsy specimens from the anterior portion of the leg and from the base of the great toe revealed the changes shown in figures 2 and 3, reported as follows:

Microscopic Study.—The specimens consisted of two sections of skin, which were similar in appearance except that one showed decided keratinization and hyperkeratosis with parakeratosis, whereas the other presented less pronounced

changes. There was no vesiculation in either section. The surface was lined with stratified squamous epithelium, which showed definite parakeratosis and keratinization. Within the upper layers of the epithelium were small focal abscesses, which contained fibrin and polymorphonuclear neutrophils. The stratum granulosum was patchy in that it was well defined and thickened in some areas and absent in others. The epithelium showed acanthosis, and the rete pegs extended

Fig. 1.—Photographs taken Aug. 22, 1947, before streptomycin therapy, showing feet, anterior aspects of the legs and nails.

down evenly in thick and slightly broadened projections. These pegs showed edema and moderate infiltration, with an occasional polymorphonuclear neutrophil and mononuclear cell. The dermal papillae presented edema and cellular infiltration, the infiltrate being composed of lymphocytes, polymorphonuclear neutrophils and plasma cells. Beneath this were increased amounts of collagen, which just beneath the epithelium showed a cellular infiltrate and moderate edema. The

few follicles and small vessels in the corium were surrounded with a mononuclear infiltrate.

COMMENT

The most striking features of this histologic lesion were parakeratosis, slight acanthosis with widening and edema of the rete pegs and the cellular infiltrate (mononuclear cells, lymphocytes and polymorphonuclear neutrophils) in the collagen of the corium. These observations were all consistent with the clinical diagnosis of keratosis blennorrhagica. Al-

Fig. 2.—Anterior aspect of leg, showing parakeratosis and microabscess formation.

though there were no true pustules, the crusted, parakeratotic epithelium contained microabscesses, which were separated from the surface by one or two layers of flattened epithelium. These, in turn, had ruptured and released their fibrin and serum contents to the surface. The predominant epithelial change in this lesion was the parakeratosis.

Beginning on August 24, streptomycin was administered in doses of 0.4 Gm. intramuscularly every four hours, for a total of 40 Gm. Within forty-eight hours after the institution of therapy the urethral discharge had completely disappeared, and on the fourth day of therapy the cutaneous lesions had begun to regress. The coronal ulceration had improved notably. By September 9, at which time a total of 40 Gm. of streptomycin had been administered, the corneal ulceration had completely epithelized, there was no urethral discharge and the skin on the legs appeared to be entirely free of lesions. Definite improvement had been noted in the keratotic palms and soles; slight improvement was evident in the nails in that

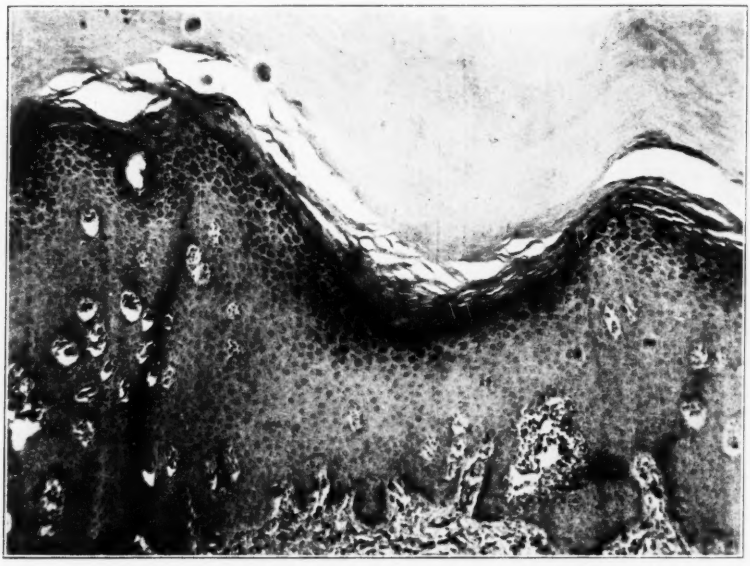

Fig. 3.—Base of great toe, showing parakeratosis and microabscess formation.

the subungual keratoses had become more brittle and were separating. Post-treatment photographs are shown in figure 4.

There were no untoward symptoms as a result of the streptomycin therapy. The prostate had become normal in size and consistency and was not tender. Cultures of the urethra for three successive days yielded no gonococci. Passage of sounds revealed a stricture of the urethra 4 cm. from the meatus. At the time of this report, the patient had been observed for a period of six weeks. During that time his cutaneous lesions had continued to regress until only the nails indicated the site of his previous involvement. He had had no symptoms whatever and had regained the weight previously lost.

SUMMARY

A soldier with keratoderma blennorrhagicum which had proved resistant to massive doses of sulfonamide drugs and penicillin was treated by means of intramuscular injections of streptomycin.

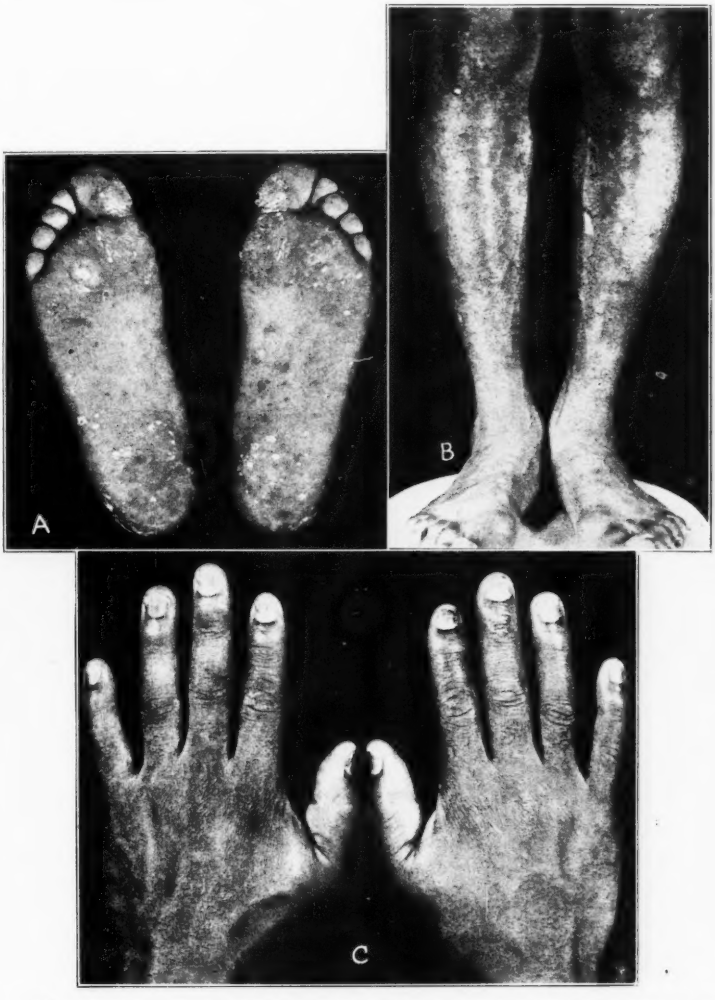

Fig. 4.—Photographs taken Oct. 8, 1947, four weeks after administration of streptomycin, showing feet, anterior aspects of the legs and nails.

Sulfonamide therapy was considered inadequate in this case when gonococci persisted in the urethral discharge and there was no improve-

ment in the cutaneous lesions after administration of more than 222 Gm. of the drug. No significant improvement was noted after administration of more than 12,500,000 units of penicillin.

Forty-eight hours after administration of streptomycin in doses of 0.4 Gm. intramuscularly there was complete cessation of the urtehral discharge. After sixteen days of therapy, during which a total of 40 Gm. of streptomycin was administered, there were complete disappearance of cutaneous lesions on the legs and unquestionable improvement on the palms and soles. Slight improvement was evident in the ungual lesions. Over a period of six weeks subsequent to streptomycin therapy, during which the patient was under observation, the remaining cutaneous lesions showed steady improvement.

CONCLUSION

Streptomycin therapy was successful in the treatment of a patient with keratoderma blennorrhagicum which was resistant to penicillin and sulfonamide drugs. This method of therapy appears to be worthy of further consideration.

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MANAGEMENT OF EMOTIONAL FACTORS IN LOCALIZED NEURODERMATITIS

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I WISH to present a simple technic for recognizing and handling the majority of the emotional problems associated with localized neurodermatitis. Most of the methods presented heretofore are too time consuming for routine use, and many dermatologists do not have access to a qualified psychiatrist. Furthermore, it is difficult to persuade patients to visit a psychiatrist. One is dealing with relatively normal people, and only a few have severe compulsions or other neuroses necessitating intensive psychiatric care.

Localized neurodermatitis is an external manifestation of chronic emotional tension and is characterized by one or more chronic, lichenified plaques located on areas which may be conveniently reached. The appearance of the plaque varies somewhat with the method used in scratching. Gentle rubbing with the dorsa of the finger nails produces a lightly hyperpigmented, ill defined patch; the interscapular region is a favorite site for this type of lesion. Ordinary rubbing and scratching produce the characteristic brownish red, slightly scaly, well defined plaque of lichenification. Intense excoriation with the edges of the nails produces an exuding, partly denuded type of plaque, often with secondary eczematization. It may not always be possible to make a definite diagnosis until the secondary infection, or the contact dermatitis from previous treatment, has subsided with bland therapy.

The itching is initiated by the emotional tension, is intense and occurs in spells or paroxysms, which are of diagnostic importance. The changes in the skin are secondary to the scratching and rubbing. A habit pattern, a vicious circle of itching, scratching and still more itching, becomes established; this is difficult to deal with on a psychiatric basis alone. On the other hand, the mere suppression or breaking of this circle by local dermatologic therapy is unsatisfactory because the fundamental cause of the disease, the emotional tension, still remains, and the percentage of recurrences is high. A combination of local treatment and some form of emotional adjustment is needed.

Read before the Section of Dermatology and Syphology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

Over one hundred years ago, Noah Worcester[1] indicated recognition of the relationship of neurodermatitis to the emotions in his book "Diseases of the Skin," which was the first dermatologic textbook to be published in America. Since then Becker,[2] Stokes[3] and others have published extensive articles on the subject. However, the emotional element is not adequately recognized and investigated by many present day dermatologists.

A statistical survey is beyond the limits of this report, but in a series of 450 cases of localized neurodermatitis I have obtained better results and had far fewer recurrences with the combined method than with local therapy alone. I am aware that in about 5 per cent of cases the mental problems are too serious or the patient's insight is insufficient to permit successful management by simple therapy. These cases should be recognized and help obtained from a competent psychiatrist while there are still sufficient tolerance to roentgen radiation and response to local measures to enable one to work concurrently with the psychiatrist, thus facilitating the patient's recovery.

PSYCHIATRIC APPROACH

A complete psychiatric history is not taken, but an attempt is made to evaluate the patient's personality while eliciting information on his dermatologic symptoms and examining his eruption. Some types with emotional problems can be recognized in a few moments and time saved by directing the questions into proper channels. External appearance can, however, be deceptive. As Becker stated in 1932,[2] "One patient may be as highstrung and temperamental as a thoroughbred race horse, and the next one as cool as the proverbial cucumber, but on further examination both are found to have neurocirculatory instability." A history of inability to relax while eating or before going to sleep, of frequent unpleasant dreams or of previous nervous breakdowns is often found. Becker emphasized that usually both parents of the patient are of the highstrung, ambitious type. Care should be taken not to pry too persistently into the patient's personal affairs and so build up resistance to further questioning, but to intersperse key queries among the routine dermatologic ones. Problems involving the patients' in-laws, husband or wife may often be exposed by casually asking, "How are things at home?" The patient's

1. Worcester, N.: Diseases of the Skin, Philadelphia, Thomas Cowperthwait & Co., 1845.

2. Becker, S. W.: Dermatoses Associated with Neurocirculatory Instability, Arch. Dermat. & Syph. **25**:655 (April) 1932; Functional Medicine from the Dermatologist's Viewpoint, J. Med. **21**:526 (Feb.) 1941.

3. Stokes, J. H.: Functional Neuroses as Complications of Organic Disease, J. A. M. A. **105**:1007 (Sept. 28) 1935.

age and marital status may make the problem obvious, as in the following case:

CASE 1.—A 62 year old widow denied all emotional causes for her neurodermatitis of seven years' duration until asked about her husband's death, whereupon she burst into tears and admitted that life had held less for her each year since her husband's death, ten years before. She was advised to take an interest in helping those around her and in looking forward to joining her husband in Heaven. Each week, while local dermatologic care was being given, a few minutes were spent in discussing and encouraging her new interests and attitudes. She developed new interest in her son and grandchildren and has had no recurrence of her neurodermatitis.

One should persevere in questioning. If the desired information is not elicited on the initial visit, try on each subsequent visit. Some patients require time to reflect before becoming articulate about their situations. The physician must appear completely unhurried; otherwise no information will be obtained. Direct questioning is necessary with the ambitious person, who may hold two, or even three, jobs, as many patients of this type will not volunteer the information that they hold more than one job.

CASE 2.—A white man aged 29, with a plaque of localized neurodermatitis of two years' duration on his right forearm, gave his vocation as that of an iron worker and stated that he worked eight hours a day for five days a week in a foundry. Insistent, direct questioning was required to bring out the information that, in addition, he worked three to five hours nightly as a filling station attendant and on weekends as a carpenter. He could give no financial reason for having so many jobs except that he had feelings of insecurity, as a carry-over from the last depression. Discontinuance of his extra jobs, reassurance about the state of his finances and local therapy brought about prompt clearing of his dermatitis.

CASE 3.—A typical area of localized neurodermatitis developed on the right calf of a man aged 28, under the stress of Army life. The lesion responded to local therapy at that time, only to recur three years later. When questioned about his work, the patient stated that he had an easy job working outside at a pottery plant, which brought him an adequate income. When asked specifically about work after regular hours, he admitted that he had been contracting, helping to build his own home for the past year. He had worked with excessive rapidity each evening to complete some part of the house before darkness. The exacerbation of his neurodermatitis coincided with the mounting problems which occurred in the building of his house. As its construction was about complete, local therapy, sedation and advice about assuming too many responsibilities in the future were sufficient to produce rapid clearing of the lesion. There has been no recurrence to date.

Another patient with a similar multiplicity of jobs admitted that his wife and four children "got on his nerves," so that he worked long hours in order to spend less time at home.

A frequent problem is the worker who hurries through everything, trying to crowd too much into a short space of time:

CASE 4.—A tool maker with localized neurodermatitis of the right ankle always arose with insufficient time to dress and eat. He attempted to gain time by driving to work at a high rate of speed. By the time he reached his plant he

was usually very nervous. His job required exacting skill, but he worked rapidly, under pressure, until the lunch hour. He habitually hurried through his meal, though he had ample time for lunch. By evening he was exhausted, and his neurodermatitis was very pruritic. He seemed to get insufficient rest from his sleep. Although he retired early, he awakened in the morning tired and nearly late for work. His troubles began during the war, when production was stepped up, but did not improve when conditions became normal. He was a heavy coffee drinker. This habit was discontinued; sedation and local care were given, and he was advised to arise early enough to dress leisurely and eat, with ample time to get to work. He was to endeavor to carry through the day in as leisurely a manner as possible. It was necessary to question this patient about his activities and to encourage him on each visit for some time in order for him to adjust properly.

A common emotional type, easily recognized, is the meticulous housewife who expends all her energy doing minor household tasks. These patients will usually admit their perfectionist trends on appropriate questioning.

Case 5.—A 58 year old housewife had been troubled for five years with a pruritic, lichenified plaque on the nape of her neck. She had had no menopausal symptoms for eight years. She admitted being nervous and was constantly fussing with her six room house. Although she and her husband lived alone, she spent from ten to twelve hours a day doing her household tasks. Her daughter stated that "Mother was constantly readjusting doilies and vases, even when company was present." "Spring cleaning" was done almost weekly. After much discussion, the mother admitted the futility of attempting to keep everything perfect and, with encouragement on each of several visits, finally made a partial adjustment. The eruption cleared with sedation and local therapy. There has been no recurrence in approximately two and a half years, at the time of writing. The daughter was seen recently as a patient, and she said that her mother was still fussy but less so than formerly. A partial adjustment is often satisfactory if the emotional tension is kept below a critical threshold.

Another feminine type is that of the woman who has assumed too many club duties, or too heavy office work in addition to her housework.

The problem of sexual incompatibility is a difficult one to evaluate, for often the patient does not admit that any problem exists; yet psychiatrists say that such maladjustments are the basis of many psychoneuroses. Some patients with so-called idiopathic vulvar, scrotal or anal pruritis may have sexual problems. In certain early cases the patient may be helped by reading a manual on sex.

Case 6.—A woman had had a pruritic, lichenified eruption of the ears and the region of the clitoris for two years. Considerable local therapy, including fifteen to twenty treatments with roentgen rays and two years of dermatologic care by other physicians, had produced little or no improvement. She drank six cups of coffee daily. Preliminary questioning revealed no emotional basis for her neurodermatitis, but queries about her family life revealed the following story. She had married at the age of 17 and since her wedding night had had a growing aversion to intercourse. Her husband was young and overly eager at the time of their marriage, and his lack of consideration, she said, had caused her to lose all

interest in sex. He was also violently opposed to having children, and she lived in constant fear of becoming pregnant. After seven years of married life her husband, apparently because of her frigidity, had had a prolonged affair with another woman. This was finally terminated at the time the patient gave birth to her second child. Her husband then began to drink heavily and would force his attentions on her while he was intoxicated, thus increasing her aversion to intercourse. He also began to insist on various abnormal sexual acts in place of normal intercourse. It was after this development that her neurodermatitis developed. Her medical bills, coupled with the cost of recurrent illnesses among her children, added financial worries ot her mounting problems. It became necessary for her husband to take an additional job to keep out of debt; as a consequence, he received only five hours of sleep nightly. When she was asked if she had considered divorce, she said that she still loved her husband and felt that he still loved her. She was referred to a psychiatrist.

TREATMENT

Patients are commonly told by their physician that they are nervous and should "go home and relax"; they try desperately to relax for a day or two, become more nervous than before and abandon the effort, as it has not been made clear to them what they should do and that weeks or even months, of persistence may be necessary to change the habits of a lifetime.

Common sense advice helps the majority of patients with localized neurodermatitis to readjust. The emotional basis of neurodermatitis is clearly explained to the patient. He is told to slow down, become more philosophic and learn to "take things in his stride," in order to get well and stay well. In short, he is advised to develop the attiude that "fifty years from now it won't make any difference, anyhow; so why worry now!" Stokes[3] emphasized the value of slogans. They are important; think what "Remember Pearl Harbor" did for us!

The intense person who always hurries through his daily tasks is advised to retire early so that he can start the day right by arising in time to dress leisurely, eat an unhurried breakfast, go slowly to work and carry on through the day in this fashion. He will find that as much can be accomplished in this way as in hurrying through the day under emotional tension, and consequently making more mistakes.

The meticulous and ambitious housewife is advised to simplify her housework by eliminating unessential work—for example, by closing off an unused room or two. The futility of being a perfectionist is discussed. She is told to work more slowly and in planning her housework to allow more time, for example, twenty-five minutes for each fifteen minute job. If she is able to obtain domestic help, she must not expend her energy criticizing every movement and method of the worker.

Good mental hygiene must be practiced; the patient is told not to sit on the fence and let his problems accumulate, but to arrive at de-

cisions as soon as it is practicable. If, for example, the problem is one of an incorrigible, drinking or philandering husband, the wife must decide either to make the best of his shortcomings and overlook them or to separate from him, instead of continually looking for a miracle.

It is necessary to give some patients a pattern for living, stressing the balanced life with adequate time for work, play, rest and religion. The physician should be humble in giving advice. He should emphasize that he is not being critical and that advice is easy to give and hard to follow, but that, nevertheless, it is important that it be followed.

I cannot emphasize too much the importance of going over the patient's problems and encouraging him on each visit. Only a few minutes are needed, as good rapport has usually been established on the initial visit. I attribute much of the success of my treatment to this.

It is impossible for a patient who is being stimulated with excessive quantities of coffee, tea or cola to slow down. This stimulation is a factor of considerable importance, but one which is frequently overlooked. Some persons are very sensitive to the action of these drinks, and even small amounts may produce undue stimulation. Abstinence from these drinks is essential.

The administration of sedatives three or four times a day in ample quantities is necessary to help the patient achieve control of himself, but this treatment should gradually be withdrawn after the itching subsides. Diphenylhydantoin sodium may be used in addition, in an effort to dull cerebral excitability when desirable.

Adequate local treatment, including roentgen therapy, should be given to help break the vicious circle of itching and scratching.

PROPHYLAXIS

On completion of treatment, the patient is advised to return for counsel if he should again become unduly upset. Often one visit, during which the patient can talk over his troubles with his doctor, will prevent the reestablishment of a stubborn neurodermatitis. This usually requires little time, as one already has the previous history and the patient has some understanding of his condition. A temporary return to sedation and the care of any new cutaneous lesion which might attract undue attention to the patient's skin are advisable. The following case is illustrative.

CASE 7.—A well to do, elderly woman with an invalided husband had been treated for two previous outbreaks of severe localized neurodermatitis following exacerbations of her husband's illness. Recently the patient returned, to say that another outbreak was imminent, as she was under great emotional tension. She had overdone by entertaining extensively during the recent holidays, and, to make matters worse, an exacerbation of her husband's condition had just occurred. She stated that she itched and tingled all over. Examination revealed only a gen-

eralized, mild dryness of the skin. Prescription of a bland cream for the dry skin, sympathetic counsel, a return to sedation and the placing of more of the responsibility for her husband's case in the hands of a competent nurse resulted both in removal of the local factor attracting attention to the skin and in release of some of the emotional tension. She is still well at the time of writing.

COMMENT

Becker,[2] Stokes[3] and others have well established the existence of the emotional basis for localized neurodermatitis. I have not attempted, in this paper, to cover all the types of problems likely to be encountered; but with the examples given I hope to stimulate physicians to the understanding that there is an emotional basis for this disease and to the realization that a few simple questions will often expose the precipitating factors and that a higher percentage of permanent cures can be achieved by helping these patients to make a better adjustment. It is not usually necessary to spend more than a few minutes obtaining the patient's history, but the patient must feel that the physician is unhurried and is giving his undivided attention. Undoubtedly, an understanding of every patient's deepest emotional problems is not always reached, but the majority of patients adjust well enough, with habit training and encouragement at the time of each visit, to live a normal life and avoid recurrences of their neurodermatitis.

The diagnosis of localized neurodermatitis is not difficult when one or more lichenified plaques are present on locations which are easily reached and typical paroxysmal pruritus of these lesions occurs. A cutaneous localizing factor is unimportant, as a normal person will soon ignore the itching of mosquito bites or of areas under a tight garter, whereas a patient with excessive emotional tension may continue to scratch and produce an area of neurodermatitis.

The menopausal type of neurodermatitis, with organic changes responsible for symptoms of emotional instability, is easily recognized. Anemia and other medical problems should be looked for, as these may prevent the patient from easily holding the pace set by others in daily life and, hence, produce anxiety and emotional tension. Localized areas of atopic dermatitis can usually be recognized and appropriate treatment given. In my series of cases of localized neurodermatitis, the incidence of a personal or a family history of allergy was no greater than in a series of cases of nonallergic conditions, including scabies.

Any patient with definite localized neurodermatitis who shows no response to antipruritic ointments, sedation and six treatments with roentgen radiation and who will admit no emotional problems should be referred to a psychiatrist, as his emotional problems are probably too deep to be handled by the dermatologist and the outcome would probably be unsatisfactory. Hours of discussion may be required merely to

bring such a patient to an understanding of his problems, and, hence, he should be treated by a psychiatrist. Patients with definite areas of localized neurodermatitis of the anal or genital region seem to be more easily handled than those with only pruritus and no demonstrable cutaneous lesions. Here, as in other areas, fungous infection and contact dermatitis should first be ruled out. Pruritis from vaginal discharge or from small amounts of irritating mucus passed, with frequent expression of gas per rectum, passage of inadequately digested stools and infection with pinworms must also be considered. Numerous, less frequent causative factors can be found listed in any modern textbook of dermatology.

SUMMARY

Localized neurodermatitis is an external expression of emotional tension. As the eruption becomes established, a tenacious habit pattern of itching, scratching and more itching develops, in addition to the emotional tension.

Most patients with localized neurodermatitis have a superficial type of emotional problem causing their pruritus. This can usually be elicited in a few minutes by simple questioning if the physician appears completely unhurried. Examples of some of the commoner types of cases are given. Treatment must be directed toward the breaking of the habit pattern of itching and scratching by local means and the patient guided to better emotional adjustment in order to reduce the number of recurrences. Elimination from the diet of coffee and other stimulants is important.

Patients with deep emotional problems should be referred to a psychiatrist immediately, so that maximum benefit can be obtained through combined psychiatric and dermatologic care.

460 Clifford Street.

ABSTRACT OF DISCUSSION

Dr. Donald J. Wilson, Omaha: We are indebted to Dr. Hubler for again calling attention to the importance of emotional factors in the genesis and continuance of localized neurodermatitis.

Patients with this disease may be divided into two groups, i.e., those with a relatively high threshold of emotional stability and those with a low threshold. The lower the threshold, the more complex and numerous are the emotional factors and the more difficult is their eradication. The cases on which the essayist reported, I believe, belong in the group with high thresholds, and the lessons he pointed out apply as well to certain cases of generalized pruritus, urticaria, pruritus ani and pruritus of the scrotum. I am particularly disturbed that I cannot always be certain to which group a patient belongs.

I agree with Dr. Hubler in his plea for early steps to diminish nervous tension, while one has the advantage of symptomatic relief with roentgen radiation,

tripelennamine hydrochloride (pyribenzamine hydrochloride[R]) cream and the mild tars to assist in building up the patient's confidence in the doctor. This is very important. It is also the time to fix in the patient's mind the importance of eliminating habitual scratching; I mean thoughtless scratching, which all these patients do. This scratching, unlike the compulsive type which occurs during an explosive episode, can be controlled with the will.

I saw one patient with a patch of chronic neurodermatitis on the lower part of one leg. He was a successful businessman from a nearby city and impressed me as being very capable and self willed. After explaining his condition to him, I gave him a prescription for a mild ointment containing tar, admonished him to let the world go by and asked him to write me in one month regarding his condition. One month later he wrote: "Your medicine did me absolutely no good because I did not use it, but your lecture was excellent. I have had almost no itching for the past three weeks, and my skin is almost well."

The patient who, after explanation of the importance of keeping his fingers away, replies, "Well, if you had it, you would scratch too," is protecting himself, enjoys scratching and will not help much in one's effort to cure him.

Dr. Hubler recommends sending to a psychiatrist those patients with a low threshold of emotional stability and whose lesions do not respond in six treatments with roentgen radiation. Because of the factor of expense and the disinclination to consult such a specialist, my patients have not received much help from such consultation and guidance.

In some persons, a patch of localized neurodermatitis may serve as a "safety valve." One such young man was under my care about a year ago. His eruption disappeared, except for residual hyperpigmentation, and he was dismissed. He is now psychoneurotic, with gastrointestinal symptoms; he is under the care of a psychiatrist and is a semi-invalid. His disorder might have followed this course regardless of the healing of his chronic dermatitis, but I do not believe I did the patient any good. Many of us who were in the service saw cases of this type.

Dr. Hubler's paper has called to our attention again some of the things so well known to us that we forget their importance, and, in so doing, he has rendered a service to the patients of all of us. We can all do much more counseling than we do, to the good of our patients.

Dr. D. E. H. Cleveland, Vancouver, British Columbia, Canada (by invitation): Dr. Hubler has emphasized that which cannot be overstressed: Whether specializing or practicing general medicine, we must keep constantly in mind the fact that we are studying and treating, not diseases or "cases," but individual human beings. As Professor Weiss of Temple University reiterated in two recently published papers, we must approach the patient with respect to the kind of person he is, where he has been, what he has done and what has happened to him to bring about his present disorder. This is practicing psychosomatic medicine.

There are many patients in dermatologic practice who suffer from emotional maladjustment, whose environment is productive of emotional tension or whose life history contains elements which result in frustrations, repressions and various conflicts; in treatment of these patients, we must give full weight to these considerations and proceed along certain well indicated lines. Dr. Hubler's wise caution against too intensive probing during the initial interview appeals to me strongly. Rough handling may result in psychic diasters.

Much of the art of medicine is nothing more nor less than the practice of psychosomatic medicine, whether we speak of it as intuition or merely as knowing

the patient. Dr. Hubler has dwelt on this factor, with respect to one skin disorder in particular, and has outlined a procedure which is simple, rational and practical.

I find myself in disagreement, however, with the major premise implicit in Dr. Hubler's summary. I cannot accept the unqualified statement that localized neurodermatitis is an external expression of emotional tension. In 1935, I read a paper before this Section pleading for Vidal's designation, lichen simplex chronicus, to be used in preference to Brocq's term, neurodermatitis. The term "disseminated neurodermatitis" as a synonym for atopic eczema is, to my mind, equally indefensible. I recognize that atopic eczema is most prevalent in the intelligent, mentally alert and psychically and physically sensitive person; how emotional tension precipitates acute exacerbations, just as infections may, and how emotionally critical periods, such as those of teething, puberty, love affairs or economic stress, are commonly marked with intensification of the cutaneous reaction. Yet, recognition of the fact that these exacerbations are activated through the neurocirculatory mechanism should not lead us to forget that, fundamentally, we are treating patients with an allergic disorder.

Recently, I reviewed a series of over 200 consecutive cases of lichen simplex chronicus. Cases in women and girls were slightly in the majority, and, as I reported in an analysis of an earlier series, the incidence was much higher among my Oriental patients. Over 10 per cent of the patients were Chinese or Japanese, and with 2 exceptions these were men or boys. Exactly half my female patients had nuchal involvement, but this was the situation in only 2 white male patients. Seventeen per cent disclosed what might be called tension states; 14 per cent gave demonstrable indications of allergy to ingested or inhaled substances as the cause; in 23 per cent the condition had occurred directly after a definite and localized trauma, either physical or from a local allergic reaction (contact dermatitis). The initial cause was not clearly determined in the remainder of the patients.

These observations present a definite obstacle to my acceptance of the doctrine that localized neurodermatitis is always an expression of emotional tension. I believe that the highest common factor in its etiology is trauma, local, minimal and oft repeated. The manner of dressing, arranging and brushing the hair over the inferior occipital protuberance, peculiar to the feminine toilet, accounts for this being the site of predilection in women. Allergy often is the cause of the initial pruritus; emotional tension often may be, and as a contributory factor frequently is, of great importance. Useful in the last instance especially, Dr. Hubler's method of approaching and handling the problem is a praiseworthy contribution to our practical knowledge.

DR. W. R. HUBLER: All localized lichenification is not, of course, neurodermatitis. As I mentioned, such conditions as contact dermatitis and atopic dermatitis must be considered. Localizing factors, such as mosquito bites and contact dermatitis with secondary neurodermatitis, are also possibilities. I have refrained from discussing these to keep the paper as uninvolved as possible.

QUANTITATIVE SEROLOGIC TITER IN POST-TREATMENT OBSERVATION OF EARLY SYPHILIS TREATED WITH PENICILLIN

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AND
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IN THIS paper an attempt is made to portray the role of the quantitative serologic titer in the post-treatment period of observation in cases of early syphilis treated with penicillin.

The penicillin used in all cases in this study was the commercial penicillin sodium; as is well known, throughout the past two years, the drug has constantly changed in the amount of impurities present and in the relative proportions of the fractions G, F, X and K.

MATERIAL AND METHOD

Since the patients chosen for consideration in this study were selected from a total of more than 700, the only criterion being a continuous and regular monthly determination of the serologic reaction of the blood for twelve months or longer, the reported relapses and presumptive cures are in no way indicative of successes or failure of penicillin therapy.

The 117 patients selected for detailed examination all had early syphilis. They were studied primarily to observe the trend of the serologic titer among patients who became clinically well, as compared with that for patients who relapsed after penicillin therapy.

The group considered clinically well had no signs or symptoms of syphilis and had reached and maintained a negative serologic titer within one year after treatment and had continued to do so. The group who relapsed included patients observed for varying periods until a serologic relapse or a seroclinical relapse occurred after penicillin therapy. Seropersistent therapeutic failures (patients whose titers remained elevated at a stationary level) were not included, as the

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Huldah Bancroft, Ph.D., Assistant Professor of Biometrics, Western Reserve University, assisted in the statistical analysis of the data.

From the Department of Dermatology and Syphilology, Western Reserve Medical School, and of the City Hospital; H. N. Cole, M.D., Director.

The work described in this paper was done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research Development and Western Reserve University, and under a grant in aid from the National Institute of Health, United States Public Health Service.

purpose of the study was to evaluate the trend of the serologic titer as an indicator of impending seronegativity or of relapse. Seronegative patients with primary syphilis were also excluded from the scope of the study.

The quantitative test used was the Lund flocculation method,[1] a macroscopic test which employs a centrifuged resuspension technic, with the Kline exclusion antigen. Four units of this test correspond to 1 Kahn unit, e.g., a dilution of 1:4 equals 1 Kahn unit; a dilution of 1:8 equals 2 Kahn units, and so on. In this study, a titer of 1:4, or 1 Kahn unit, was assumed to be borderline, and a reading of 1:2 or 1/2 Kahn unit, was considered to indicate a negative reaction, as were all readings "under 1 unit."

OBSERVATIONS

GROUP 1.—In the first group, 35 patients were followed for at least one year. The penicillin treatment schedule employed was 40,000 units every six hours for thirty injections, a total of 1,200,000 units.

Of this group of 35 patients with early syphilis who were seropositive before institution of penicillin therapy, 17 became seronegative and clinically well within one year after treatment. The spinal fluid findings were normal for all patients in this group. Seropositive patients with primary syphilis became seronegative more rapidly than patients with secondary syphilis. The peak at which the serologic titer became negative was in the second and third months of treatment.

Of particular interest was the fluctuation of the quantitative titer from month to month after penicillin treatment. Shaffer[2] called attention to this feature in a previous study, and observation of these cases substantiated his findings. These fluctuations from negativity, usually of 1 to 2 dilutions, equivalent to 1 to 2 Kahn quantitative units, followed a definite pattern; they lasted only one or two months, never showed a sustained or constantly increasing titer and reverted to permanent negativity within two months.

Of the 17 patients who became seronegative and clinically well within one year after treatment, 17 per cent became seronegative, followed by a fluctuation in the titer to positivity before seronegativity was resumed.

Of the patients with relapses, 33 per cent obtained an initial negative titer before relapse occurred.

GROUP 2.—The second group comprised a total of 61 seropositive patients with early syphilis who received a total of 1,600,000 units of penicillin, administered in a dosage of 20,000 units every three hours for eighty injections, over a period of ten days.

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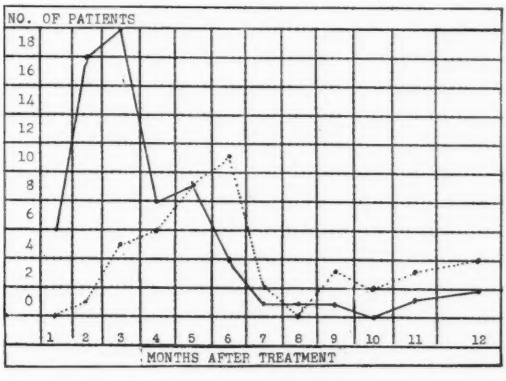
1. Lund, H.: Titration of Traces of Reagin: Technique of Flocculation Using Maximal Serum Proportions with Secondary Recovery of Antigen, Am. J. Syph., Gonor. & Ven. Dis. **26**:1-15 (Jan.) 1942.

2. Shaffer, L. W.: Intensive Arsenotherapy of Early Syphilis, Arch. Dermat. & Syph. **52**:147-154 (Sept.) 1945.

Forty-three patients appeared clinically well, and their serologic titers became consistently negative during the period of observation; 63 per cent of this group arrived at seronegativity within three months, and a total of 93 per cent attained seronegativity within six months. It was observed that 16 patients, or 37 per cent, became seronegative, followed by a fluctuation to positivity in the titer before seronegativity was resumed and maintained; 27 patients, or 63 per cent, demonstrated no fluctation after attaining seronegativity.

Eighteen patients comprised the group who had relapses; of this number, 11 had seroclinical and 7 serologic relapses only. The peak of the relapses, comprising 12 cases, or two thirds of the group, occurred within the first six months after therapy. In these cases, a gradual rise



This composite graph of all the cases in the study reveals the month in which the quantitative serologic titer became persistently negative in the group of well patients (solid line) and the month in which a relapse occurred among patients in the group with relapses (line of dots).

in the serologic titer preceded the relapse. In 39 per cent of the cases in this group, a sudden drop to negativity in the titer was observed within two months after therapy. However, in no instance was this maintained longer than one month, after which the increase in positivity of the quantitative reaction was either gradual or abrupt.

GROUP 3.—The third group, of 21 patients, received 2,400,000 units of penicillin, administered in a dosage of 20,000 units every three hours for one hundred and twenty injections over a period of fifteen days. Of these 21 seropositive patients with early syphilis, 11 became seronegative and clinically well at the end of one year's observation, and 10 patients had a relapse.

In the well group, 10 of the 11 patients were seronegative at the end of five months, the peak occurring in the third month of treatment. The quantitative titer in 45 per cent of the group revealed a temporary rise of from 1 to 3 dilutions, equivalent to 1 to 3 Kahn quantitative units. This rise was never sustained, and the patients dropped back to seronegativity within one to two months. In 55 per cent of the group there was no fluctuation in the quantitative titer; when seronegativity was achieved, it was maintained throughout the period of observation.

Of the 10 patients in the group with relapses, 3 had seroclinical relapses and 7 serologic relapses. Eight of the 10 patients had relapses within six months after the completion of penicillin therapy.

Fluctuations in Titer After Treatment with Penicillin in the Well Group and in the Group with Relapses

Treatment Group; Penicillin Dose, Total Units	No. of Seronegative Patients	Per Cent of Clinically Well Patients Obtaining Positive Titer After Initial Negative Titer	No. of Seropositive Patients	Per Cent of Patients with Relapses Obtaining Initial Negative Titer Before Repaise
Group 1 1,200,000 units	17	17	18	33
Group 2 1,600,000 units	43	37	18	39
Group 3 2,400,000 units	11	45	10	20
		Average: 33		Average :30.6

On examination of the individual titers in the group with relapses, it was observed that 20 per cent of the patients obtained a seronegative titer very early in the course of monthly post-treatment determinations. Again, this was of short duration, a maximum of two months, after which the titer became elevated, according to the pattern noted and described in both the preceding series analyzed in this study.

The following data indicate the pattern formed by the fluctuation of the quantitative titer from month to month in the post-treatment observation period. The data presented demonstrate that there is a fluctuation in the group of well patients, just as there is in the group of patients with relapses. In the well group, it is a temporary increase in titer toward seropositivity, with return to permanent negativity within a maximum of two months; in the group with relapses, it is a brief drop in titer toward seronegativity, followed by a quick and sustained elevation of titer until a relapse ensues (table).

SUMMARY

A series of 117 patients with early syphilis treated with penicillin were followed with monthly determinations of serologic titer and clinical examinations for one year, or until a relapse ensued. Of this series, 71 patients became seronegative and clinically well by the end of one year; 46 patients had either a serologic or a seroclinical relapse.

This series was studied primarily and solely for the quantitative serologic response to penicillin therapy of early syphilis. The patients were selected from a total of 700 treated according to the assigned schedules and chosen solely on a basis of regular and continuous monthly post-treatment observation; therefore this paper and is contents cannot be construed as an index of the efficacy of penicillin therapy in early syphilis.

Of the 71 patients who were considered clinically well and seronegative, the serologic titer became negative in 56 per cent within three months and in 91 per cent within six months after treatment.

Of the group with relapses, 69 per cent had relapses within six months and 80 per cent within nine months after treatment. Several months prior to the relapse, a gradually increasing or sustained high titer was seen in every case, thus forecasting the ultimate relapse.

In 33 per cent of the well patients examined, there was a fluctuation in the quantitative titer after the achievement of negativity. The fluctuation varied from 1 to 3 Kahn units. A characteristic feature was the return to permanent negativity within two months.

Paralleling this fluctuation in titer in the well group, 30 per cent of the relapsed group attained temporary negativity. This drop to negativity was usually sharp, and then, within two months, the titer was again high or was increasing steadily. It is concluded that in cases of the penicillin treatment of syphilis complicating pregnancy, the quantitative serologic titer serves one of its most valuable roles. A monthly or bimonthly quantitative test on the newborn will indicate whether the positive reaction of the cord blood, or the serologic titer at birth, was due to an active syphilitic infection or was attributable to the transfer of maternal reagins through the placenta to the fetal circulation.

A single negative serologic titer during the early months of follow-up observation is not of great prognostic significance, for it has been seen that this occurred in approximately one third of the cases in the group with relapses.

Western Reserve University.

LICHEN PLANUS IN SUBTROPICAL COUNTRIES

Study of an Annular Type with Inverse Localization (Uncovered Surfaces of the Skin)

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EVEN IN a moderate climate, lichen planus presents a variegated appearance, although it usually is associated with well defined primary efflorescences. In subtropical regions, however, if a physician sees lichen planus during its further development, he meets manifestations which, although presenting a specific picture, may show such a degree of variation that dermatologists from elsewhere would be unable to make a correct diagnosis.

GENERAL CONSIDERATIONS

In this paper, a special form of lichen planus will be described. This type of the disease, which occurs in the Middle East, particularly in Palestine, offers new problems in many respects. The studies are based on the entire number of patients with the disease seen at the Dermatological Outpatient Department of the Rothschild-Hadassah University Hospital, Jerusalem, since the year 1930. Approximately half of the patients visiting the clinic are Jews of European extraction; the other half are Jews from oriental countries, who have, as a rule, dark complexions.

Apart from the ordinary types of lichen planus, such as acute, annular, verrucous, pemphigoid and other rarer varieties which, typically, are localized, there exists in the Middle East a type in which the lesions develop almost exclusively on the exposed parts of the skin. In this form of lichen planus, recurrence is the rule as soon as the patients are exposed to sunlight, whereas spontaneous remission is likely to occur in the rainy period. Diagnosis becomes particularly difficult if the lesions, in the form of annular pigmented patches, are confined to the face, particularly the forehead, since such localization generally is considered to be rare.

From the Dermatological Department (Head: Dr. A. Dostrovsky) of the Rothschild-Hadassah University Hospital, Jerusalem.

MATERIAL

During the years 1930 through 1946, a total of 131 patients who had lichen planus were observed (approximately 0.2 per cent of all patients with dermatologic disease).

Eighty of the patients had the classic type of lichen planus; 51 patients had the special variety of lichen planus to be considered herein. In both groups, female patients outnumbered male patients: of 80 patients who had the typical form of lichen planus, 54 were women and 26 were men; of the 51 who had the special form, 31 were women and 20 were men.

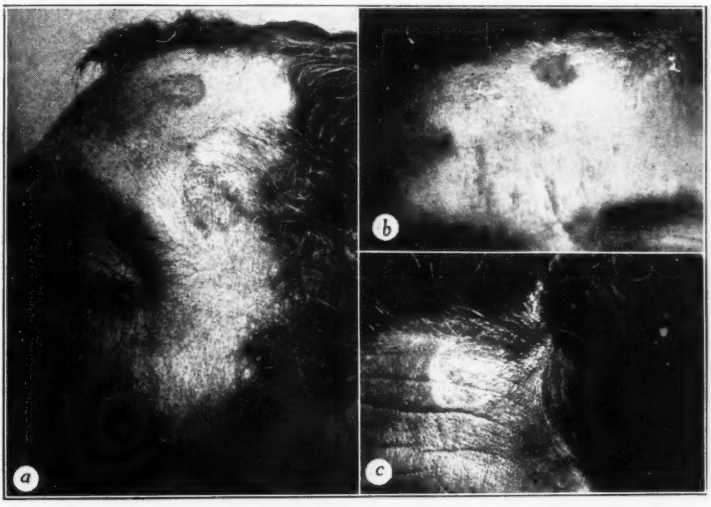

Fig. 1.—(*a*) A 41 year old patient from Iraq, with the annular type of subtropical lichen planus confined to the forehead and nape of the neck. (*b*) The patient in case 3, in whom lesions of the annular type of lichen planus occurred simultaneously with summer prurigo on the extensor aspect of the upper extremities and the exposed part of the chest; this view shows the scars of variola, which the patient had had in her childhood. (*c*) Isolated annular lesions of subtropical lichen planus, with little pigmentation, on the forehead of a dark-complexioned patient from Bagdad. The infiltrated border appears to be hypopigmented.

MORPHOLOGIC ASPECTS AND LOCALIZATION OF LESIONS

Among the aforementioned 51 patients, the lesions were almost entirely of the annular type. In moderate regions, lichen annularis may occur on any part of the body, but it is especially likely to appear in the mucous membranes of the mouth and the genital organs. In the special type of lichen planus occurring in the Middle East, frequently the first appearance is a pigmented brown patch, without any infiltration, in which, in

the course of time, there develops a delicate elevated edge, usually less decidedly pigmented than the center. Occasionally, conditions may become reversed, so that a pigmented spot remains after the infiltrated edge has disappeared. As a rule, several stages are encountered simultaneously (fig. 1). These lesions may appear singly or multiply.

It is especially by their localization (table 1) that these lesions are distinguished from the lesions of the customary types of lichen planus.

Moreover, among the patients who had the subtropical type of lichen planus, 17 had involvement of the forehead alone, 22 had involvement of the forehead, together with the extremities, 2 had involvement of the forehead, along with the mucous membrane of the mouth, 2 had involvement of the forehead, face and genitals, 2 had involvement of the face and trunk, 3 had involvement of the extensor surfaces of the extremities alone and 2 had involvement of the extremities, together with the mucous membranes of the mouth and the genitals.

Hence, it is seen that, whereas typical lichen planus ordinarily localizes at the extremities, the trunk and the mucous membrane of the mouth, the subtropical form of lichen planus is likeliest to involve the forehead, the backs of the hands, the extensor surface of the upper extremities, the cheeks and the lower lip.

In table 2 it appears that subtropical lichen planus is a disease of persons in the lower age groups. Whereas, among those who had typical lichen planus, no more than 2 patients (2.5 per cent) were less than 20 years old; 14 patients (27.4 per cent) who had the subtropical type of lichen planus were in this age group. This difference becomes even more striking if the comparison is made in both groups up to the age of 40 years. Of the 51 patients who had subtropical lichen planus, 6 (11.8 per cent) were more than 40 years old, whereas of 80 patients who had the classic form of lichen planus, 48 (60 per cent) were more than 40 years old. Among the latter 48 patients were 21 (26.3 per cent) who were between 60 and 80 years old. The youngest patient who had classic lichen planus was 9 years old; the oldest was 77 years old. The youngest patient who had the subtropical form of lichen planus was 4 years old, and the oldest was 57 years old.

The average age of the patient at the onset of classic lichen planus was 47 years. The average age of the patient at the onset of the subtropical form of lichen planus was 28 years.

In table 3 it is seen that 56 of the patients who had classic lichen planus were Jews who had emigrated from Europe. Moreover, of the 14 patients with classic lichen planus who were born in Palestine, 12 had European parents, which indicates that in our series of 131 cases, classic lichen planus occurred in only 12 persons of Oriental or Middle Eastern birth or extraction.

TABLE 1.—*Localization of Lichen Planus in One Hundred and Thirty-One Cases*

Site	Localization (Number of Cases)	
	Classic Lichen Planus	Subtropical Lichen Planus
Head, hairy part of	—	1
Forehead	2*	41
Temple	—	6
Ear	—	2
Cheeks	2*	12
Eyelids	—	9
Nose	—	9
Neck, nape	2	5
Lip, lower	4	13
Mouth, mucous membrane	22	8
Extremities, upper	56	17†
Hand, back of	14	21
Extremities, lower	54	6†
Trunk	37	2
Genitals	10	4
Nails	1	—

*In each of these cases the entire body was excessively involved, including the forehead and cheeks.

†On the upper extremities only the extensor surfaces were affected, whereas, on the lower extremities, lesions were seen in the region of the knees and on the backs of the feet.

TABLE 2.—*Distribution of Lichen Planus, According to Age, in One Hundred and Thirty-One Patients*

Age (Yr.)	Lichen Planus (Type)			
	Classic		Subtropical	
	Number	Percentage*	Number	Percentage†
Through 10	1	1	3	6
11 to 21	1	1	11	22
21 to 31	10	12	20	39
31 to 41	20	25	11	22
41 to 51	18	23	5	9
51 to 61	9	11	1	2
61 to 71	15	19	—	—
71 to 81	6	8	—	—
Totals	80	100	51	100

*Of 80 patients with classic lichen planus.
†Of 51 patients with subtropical lichen planus.

On the other hand, only 7 patients with the subtropical form of lichen planus were from Europe. If, then, the 2 patients who were born in Palestine but were of European parentage are added, it is seen that the subtropical type of lichen planus occurred in only 9 persons who were not of Oriental or Middle Eastern birth or extraction. All these patients, however, had been living in Palestine for many years.

TABLE 3.—*Countries of Origin of One Hundred and Thirty-One Patients with Lichen Planus*

Country	Lichen Planus (Type)			
	Classic		Subtropical	
	Number	Percentage*	Number	Percentage†
Palestine	14	18	18‡	35
Other Middle Eastern and Asiatic countries	10	12	21	41
Africa	—	—	5	10
Europe	56	70	7	14
Total	80	100	51	100

*Of 80 patients with the classic form of lichen planus.
†Of 51 patients with the subtropical form of lichen planus.
‡Of the 18 patients who were born in Palestine, the parents of 16 came from subtropical countries and the parents of 2 came from Europe.

TABLE 4.—*Season of Onset of Lichen Planus (by Cases)*

Lichen Planus (Type)	Season			
	Winter	Spring	Summer	Autumn
Classic	20	11	14	23
Subtropical	6	11	22	6

It appears, therefore, that the subtropical form of lichen planus is preponderantly a disease which attacks persons from warm countries who have a dark complexion, whereas typical lichen planus occurs among persons from Europe, the Middle East or Asia, although it more frequently attacks Europeans.

ONSET OF DISEASE

Since the majority of the patients reported that the lesions were particularly likely to appear or to become intensified after exposure to sunlight and that recurrences were the rule in spring and summer, we endeavored to ascertain in what season eruptions were likely to develop (table 4). Reliable information could not be obtained from all the

patients; hence, table 4 is based on information which could be checked or which appeared to be valid.

Whereas, it appears that lichen planus of the classic type may occur at any season, without special concentration of the incidence in any one of them, the large number of cases in which subtropical lichen planus occurred in the spring and summer is reported herein for the first time. However, since the climate of Palestine is characterized by many sunny days in autumn and winter, as well, this particular seasonal distribution does not allow of as clearcut conclusions as would be the case in a moderate climate.

Recurrences, however, were particularly recorded by us in summer, especially among patients who led an outdoor life, whereas the disease never recurred in the rainy season.

DURATION OF DISEASE

Among 51 cases of classic lichen planus, the duration of the disease was one year in 38 cases, and two years in 6 cases. In 7 cases the duration was more than two years, the longest period being thirteen years.

So far as the subtropical form of lichen planus is concerned, the duration of the disease was less than a year in 18 cases, was two years in 5 cases and was longer than two years in 12 cases. The longest duration was seven years. Thus, practically half the patients with the subtropical form had the disease for more than a year, whereas, of those who had the classic type, the majority were cured before a year had elapsed. It should be added, however, that the classic type likewise seems to be more resistant to treatment in Palestine than in moderate climates.

SYMPTOMATIC ASPECTS OF SUBTROPICAL LICHEN PLANUS

Itching, which is an important symptom of ordinary lichen planus, plays a minor part in the subtropical type. It does not affect the patient's general health.

LABORATORY ASPECTS OF SUBTROPICAL LICHEN PLANUS

General Procedures.—Wassermann and Kahn reactions were obtained in 13 cases; all reactions, however, were negative.

Examination based on the method devised by Beckh, Ellinger and Spies[1] was carried out twelve times for 9 patients, 3 of whom were examined both before and after exposure to sunlight. The results of examination were positive in 4 instances; in 6 they were doubtful, and in 2 they were negative.

1. Beckh, W.; Ellinger, P., and Spies, T. D.: Porphyrinuria in Pellagra, Quart J. Med. **6**:305-319 (July) 1937.

Urinalysis for coproporphyrin was carried out fifteen times for 12 patients.[2] The method was that of Dobriner and Rhoads.[3] In all cases, values for the excretion of coproporphyrin in the urine were within normal range, which means that in no instance was a value higher than 120 micrograms within twenty-four hours.

In 7 cases the urine was examined for urobilinogen, the result being negative in all except 1.

In several cases, moreover, tests of hepatic function were made, determinations of the content of cholesterol were made and the blood picture was studied, but all these procedures yielded normal results.

For 9 of the patients, the erythema dose of irradiation with a quartz lamp was determined on a portion of healthy skin, and the reactions were compared with those obtained among 10 control patients. Increased sensitivity to ultraviolet rays could not be established thereby. Moreover, the same procedure carried out on portions of affected skin of the same patients likewise did not demonstrate increased sensitivity, as compared with reactions observed in unaffected parts.

Isomorphic Irritation Effect.—In 4 cases, an attempt was made to obtain a Köbner effect in affected, as well as normal, portions of skin, by scratching with a needle. During an observation period of four weeks, no isomorphic irritation effect could be observed in any case. This is not surprising, since the phenomenon is confined almost entirely to acute lichen planus and practically never can be elicited in the localized types of lichen planus, which the patients under consideration had.

Histologic Examination.—Biopsy was performed thirty-four times among 27 patients. Specimens of tissue usually were taken from the face and extremities. From 7 patients tissue was taken from two sites simultaneously. The histologic picture was, according to Professor Franco, that characteristic of lichen planus. In the majority of the sections slight hyperkeratosis and decided thickening of the granular layer were noted (fig. 2). The normal borderline between epithelium and cutis generally could not be distinguished in the infiltrated areas, and the normal structure of the basal cell and squamous cell layers was disturbed. Interspersed between the cells of the epidermis were other cells which apparently derived from the cutis. The rete ridges usually were thin and short; occasionally, particularly in sections of tissue from the forehead, they were practically absent and the border toward the cutis formed a straight line.

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2. Dr. Rosenthal performed the urinalyses in these cases.

3. Dobriner, K., and Rhoads, C. P.: The Quantitative Determination of Urinary Coproporphyrin, New England J. Med. **219**:1027-1029 (Dec. 29) 1938; The Porphyrins in Health and Disease, Physiol. Rev. **20**:416-468 (July) 1940.

The cellular infiltration was confined to the papillary body and the upper part of the cutis; it consisted preponderantly of lymphocytic elements, intermingled with isolated polymorphic cells. Here and there gaps appeared underneath the epithelium, and there was hyaline degeneration in the cutis. At several places, accumulations of pigment were noted in the basal cell layer, appearing as minute granules; in the upper layer these accumulations formed large clusters.

TREATMENT OF SUBTROPICAL LICHEN PLANUS

The therapeutic effect of bismuth and arsenic compounds was unsatisfactory. In 18 cases, therefore, grenz rays were employed, with the result that in 10 cases the lesions disappeared. Three patients were improved by such treatment; the condition of 1 did not respond, and 4 patients did not report for final examination and evaluation.

The doses used were between 300 and 400 r, with 10 kilovolts, which is equivalent to a half-value layer of 0.027 mm. of aluminum. This dose was administered two or three times, and at intervals of one week to two weeks.

It was seen that during treatment with grenz rays the elevated edge of the lesion was the first to disappear, whereas, at that particular time, pigmentation in the center even increased in intensity. It was only one month to three months after the infiltration vanished that pigmentation, similarly, was likely to subside. Occasionally, it was necessary to resort to bleaching agents to hasten depigmentation.

Irradiation had an entirely localized effect, however. In 4 patients the development of new lesions was observed in other sites. When recurrences developed during the ensuing summer, they usually spared the portions that had been irradiated. Compared with the results of treatment with grenz rays in the customary types of lichen planus,[4] the results of this type of treatment in the subtropical form seem to indicate that the latter form responds more readily to treatment with grenz rays than do the others.

REPORT OF CASES OF SUBTROPICAL LICHEN PLANUS

CASE 1.—A boy 13 years old, born in Iran, never had been seriously ill until four months before we saw him. At that time he had noticed lesions on his forehead, the backs of his hands and, two months later, on his left leg.

At examination on June 29, 1944, the patient was observed to have facies oleosa. Numerous comedos and milia were seen in the region of the nose. The skin of the patient was dark brown.

In the middle of the forehead, the patient had a scar, caused by an injury four years before. This scar was surrounded by a network of bluish red papules,

4. Kalz, F.: Theoretic Considerations and Clinical Use of Grenz Rays in Dermatology, Arch. Dermat. & Syph. **43**:447-472 (March) 1941.

partly coalesced and appearing in annular arrangement. To the right of this scar was an annular lesion, 1.5 cm. in diameter, with a slightly elevated edge, consisting of a multitude of minute nodules of a whitish blue tinge. On the right side of the forehead was a network of shining papules. In addition, all over the skin of the forehead were delicate ring-shaped pigmentations, in no other way distinguished from the normal skin. On both sides of the nose, proceeding to the lower eyelid,

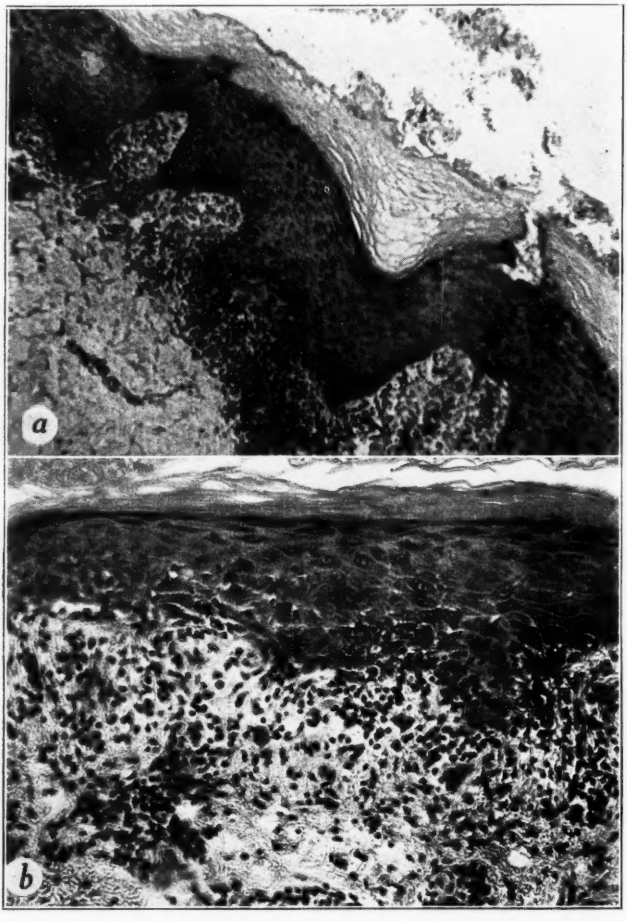

Fig. 2.—(*a*) Section of tissue from the back of the hand of the patient in case 1, showing hyperkeratosis, thickening of the granular layer and lymphocytic infiltration in the upper part of the cutis, partly penetrating to the epidermis (× 80). (*b*) Tissue from the forehead of the same patient, showing that the infiltration has penetrated from the upper part of the cutis into the epidermis (× 190).

clusters of bluish papules were arranged in lines, more decided on the right than on the left side. On the lower lip, at the border between the red part and the mucous membrane, were three small pigmented circles, although the upper lip was free of lesions. The hard palate contained whitish blue dots, but the soft palate showed no changes. The backs of the hands were covered with small polygonal bluish white nodules with Wickham's strips, extending up to the region of the wrist; the palm was normal. On the back of the right hand were confluent lesions forming a verrucous plate, the center of which exhibited a tendency to heal with whitish scales. The rest of the extremities, as well as the trunk, showed nothing abnormal, except for an annular lesion, 2 cm. in diameter, presenting the same aspect as the lesions of the forehead and situated 3 cm. beneath the left knee. This lesion had appeared only after the patient had taken to wearing summer shorts.

Results of examination of the blood were normal. The reaction to the Beckh-Ellinger-Spies test was positive on one occasion; on another it was negative. Three determinations were made of coproporphyrin in the urine; the values established were between 35 and 50 micrograms within twenty-four hours.

Specimens for biopsy were taken from the forehead and the verrucous patch on the back of the hand. The tissue from the back of the hand contained pronounced hyperkeratosis (fig. 2*A*). The granular layer consisted of four to eight rows. Where the cutis showed infiltration, the malpighian rete was thickened. The normal structure of the basic layer was disturbed at these sites, with immigration of numerous cells. In the uppermost layer of the cutis was infiltration composed mainly of lymphocytic elements. The elastic layer was absent in the areas of infiltration.

In the section taken from the forehead (fig. 2*B*), the changes were essentially the same as those noted on the hands, although the epidermis as a whole seemed thinner. Here and there it was almost atrophied. In this section hyperkeratosis was, however, less pronounced and there were more pigment granules than in the section taken from the hand.

After scratching with a needle at the forehead and back, no isomorphic irritation effect was noted during the course of one month. Neither could, at the same sites, any difference in reaction to the erythema dose of ultraviolet rays be established.

Treatment consisted of irradiation with grenz rays, with a total of 900 r, in doses of 300 r, radiation factors being the same as those previously mentioned. The irradiated lesions healed in the course of eight weeks. At the same time, several others developed on the forearms. The untreated lesion of the region of the knee became three times the original size. In November, the patient noticed a new lesion at the nape of the neck where the collar did not cover the skin. During the course of the winter months all the lesions paled distinctly, without, however, disappearing completely.

Summary of Case.—In a dark-complexioned boy from Iran, annular lesions appeared on the forehead and face simultaneously with typical lichen planus papules on the back of the hands. A similar lesion was noted in the region of the left knee after the patient had started to wear summer shorts.

CASE 2.—This report is illustrative of recurrences of subtropical lichen planus in summer. The patient was a boy 18 years old, who was born in Palestine and whose parents had immigrated from Iran. He registered at our outpatient clinic

for the first time in 1941, presenting lesions on the backs of his hands and forearms, which he had had for five years. He also had lesions on his face, that had been present for five months. The first lesion, he said, had appeared on the forehead and had been followed rapidly by the development of those on the face. During the winter months the lesions would become less distinct and were even likely to disappear partly. They would reappear regularly, however, in summer.

At examination on May 9, 1941, the entire forehead, as well as the vicinity of the eyes and eyelids, was studded with annular lesions, darkly pigmented (brown) in the center, with slightly elevated whitish blue edges. On the backs of the hands were the typical nodules of lichen planus.

The histologic aspects of sections of tissue were those characteristic of lichen planus. Treatment consisted of the administration of grenz rays to the affected sites in two doses of 400 r each, at an interval of ten days. Within the course of six weeks, the infiltrated edges had disappeared. After half a year all the lesions had completely healed.

On April 28, 1943, the patient returned, presenting lesions on the face. Three applications, of 300 r each, of grenz rays caused the lesions to disappear.

On September 8, it was seen that a new lesion had developed on the right forearm. This lesion also disappeared after the use of grenz rays. The patient was examined at various times during another year, during which time no new lesions developed.

Summary of Case.—In an 18 year old patient of dark complexion, whose parents had immigrated from Iran, lesions developed on the exposed parts of the body. These lesions appeared with seasonal fluctuation during the course of seven years. Whereas the annular type of lichen planus prevailed on the face, there were nodules typical of the classic form of the disease on the backs of the hands. During the rainy season the lesions partly disappeared. The local response to treatment with grenz rays was satisfactory.

Case 3.—This case illustrates a combination of lichen planus of the forehead with prurigo aestivalis-like efflorescences on the upper extremities. The patient, a woman 24 years old, was born in Bagdad, Iraq. She had been living in Palestine for twenty-two years at the time we saw her. At the age of 4 years she had had smallpox, and the scars were still evident on the face. When she registered at our outpatient department, she was in the fifth month of pregnancy and had four children, all alive and healthy. She said that the present disorder had begun on the forehead, seven months previously. At examination on Feb. 1, 1946, the patient was observed to have two patches in the middle of the forehead, one at the hair line and the other at the right side of the forehead (fig. 1*B*). Both lesions were oval and grayish black, with slightly elevated edges and mild infiltration. The edges had slightly shining whitish blue surfaces. In the oral cavity, there was, on the right side, at a level with the posterior molar teeth, a whitish patch with slight erosion of the mucous membrane. The reactions to the Wassermann and Kahn tests were negative. The value for coproporphyrin in the urine was 50 micrograms in twenty-four hours. The result of the urobilinogen test was positive; results of the urorosein, Takata-Ara and cephalin flocculation tests were negative. The value for diastase in the blood was 62 units; for glucose, it was 73 mg. per hundred cubic centimeters of blood; for total proteins, it was 6.52 Gm. per hundred cubic centimeters of serum. The value for euglobulin was normal.

Histologic examination of a specimen of tissue from the forehead showed distinct hyperkeratosis. The granular layer was thickened, and the rete ridges were small; here and there they were entirely absent. Just underneath the epidermis were accumulations of densely concentrated lymphocytic cells and a few plasma cells, occasionally penetrating into the basal cell layer. The appendages of the skin were normal.

In the meantime (up to March 2), while the patient had received no treatment of any kind, numerous fresh lesions had appeared, so that the entire forehead had become studded with ring-shaped lesions. There were, furthermore, small flat polygonal nodules on the forehead. The skin was slightly red to as far as both sides of the nose. A nodule typical of lichen planus was noted on the left cheek. On the external aspects of the upper and lower arms, numerous excoriations were noticeable; several of the nodules had been scratched open and were covered with sanguineous crusts. Similar lesions were seen at the exposed parts of the neck and chest. The lower extremities showed nothing abnormal. The patient complained of troublesome itching, which she said that she noticed particularly after she had worked out in the sunlight.

The patient was seen again on July 5. A month previously, the patient had given birth to a healthy child. On July 5, it was seen that the cutaneous manifestations on the forehead had become more intense, with numerous fresh lesions.

The patient now received three doses of grenz rays, of 400 r each, on the entire region of the forehead. Six weeks after treatment was started, the infiltrations disappeared and the entire forehead showed a uniform dark pigmentation. During the subsequent few months, this pigmentation gradually subsided, partly assisted by bleaching agents.

Summary of Case.—In a woman born in Bagdad, annular lesions of lichen planus developed on the forehead simultaneously with prurigo aestivalis-like efflorescences of the arms and neck.

CASE 4.—This case illustrates extreme development of the cutaneous manifestations of the subtropical form of lichen planus in a Negro stationed with the Army in the Middle East, where he had been for four years.[5]

The patient was 27 years old. He was born in Kenya, East Africa. He could give no information as to earlier diseases. He presented a cutaneous disease that he had had for four years on the forehead, neck and trunk and for two years on the lips. For the previous year he had had a lesion on a vaccination scar on his right upper arm. The lesions are shown in figure 3. On the left side of the forehead, from the eyebrows up to the hair line, the patient presented round or oval patches, which were more darkly pigmented in the center than on the rest of the skin. The edges of the patches were distinctly elevated, with less pigmentation, and were whitish blue. Similar lesions were present on both cheeks. At the nape of the neck behind the ears, these lesions coalesced to form large areas extending from the hair line in wide bands down to the auricle and, from there, stretching down in triangular shape to the second thoracic vertebra. This whole deeply pigmented area was surrounded by a bluish white elevated edge. Another lesion of this type was seen at the back of the auricle. In the clavicular region were isolated ring-shaped lesions of varying size. Below the clavicle a group of nodules ran in a bow-shaped line—as in herpes zoster—from above the mamilla to the axilla up to the posterior axillary fold. Here the lesion was composed of small flat

5. Major Brass, Royal Army Medical Corps, placed this case at our disposal.

nodules, some of which had a slight depression in the center. On the left upper arm, an annular plaque was seen on a vaccination scar; a similar plaque was evident above the olecranon process. Small lichen planus nodules were noted on the dorsal and volar aspects of the forearms, as well as on the backs of the hands. The lips, particularly the lower lip, were studded with delicate ring-shaped lesions, which had bluish gray edges. On each side of the mucous membrane of the mouth

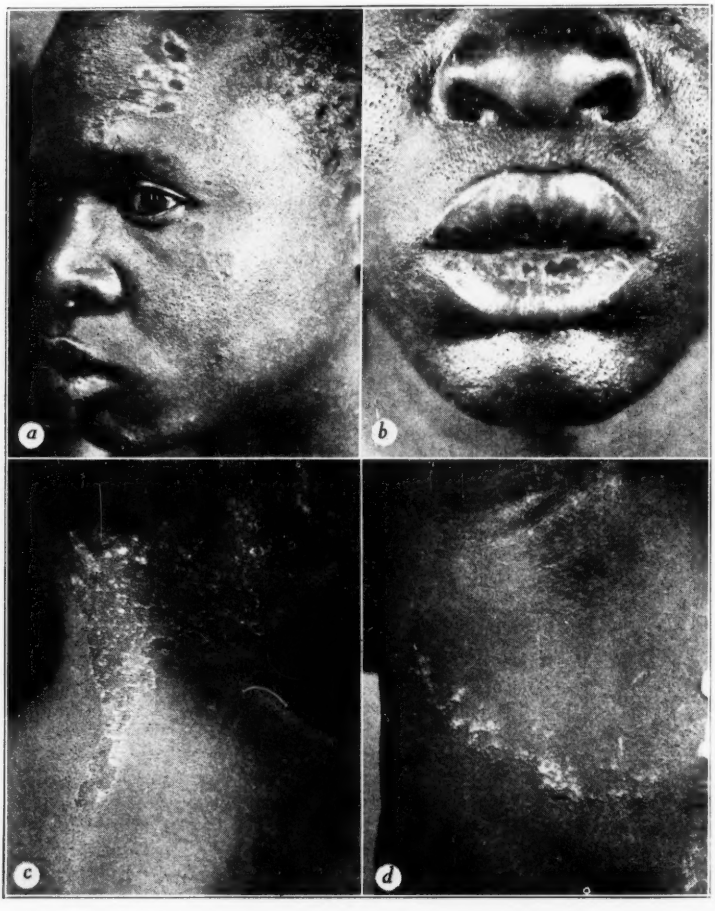

Fig. 3.—(*a*) Characteristic lesions of the subtropical form of lichen planus on the forehead and cheeks of the patient in case 4. (*b*) Same patient as in *A*, showing the same kind of annular lesions on the lips. (*c*) Same patient, showing the confluence of the annular lesions, forming a maplike pattern on the neck and nape of neck; the center shows darker pigmentation than the normal skin, whereas the infiltrated edges seem to be lighter. (*d*) Same patient, showing simultaneous zosteriform distribution of lichen planus on the chest.

was one pigmented ring. On the outer aspect of the left upper arm, a lichenified band (Köbner phenomenon, with scratching marks?) was noted.

The reactions to the Wassermann and Kahn tests were negative, as were the results of the Takata-Ara and the cephalin flocculation tests. The value for diastase in the blood was 66 units; that for glucose was 0.92 mg. per hundred cubic centimeters of blood; that for coproporphyrin in the urine was 49 micrograms in twenty-four hours. There were traces of urobilinogen; the result of the urobilin test was negative. Urorosein was not determinable, because of the interference of other pigments (black-green).

Specimens of tissue for biopsy were taken from one of the ring-shaped lesions of the chest and from nodules underneath the axilla and forearm. In all of them the histologic structure was that of lichen planus.

Summary of Case.—In a Negro, 27 years old, from Central Africa, two separate types of lesions were noted. First, lesions of oval outline, with dark pigmentation in the center and elevated bluish white edges, were seen. Second, flat nodules, some of them with a central depression, of polygonal shape, were observed. The lesions were preponderantly concentrated in areas exposed to the sun, except for a zosteriform band on the chest, where the skin usually was covered. This, then, was a dyschromic type of lichen planus, with photogenic localization of the annular type only, whereas, the nodular type of the disease appeared on the covered parts of the body.

COMMENT

The occurrence of lichen planus among the total number of patients with dermatologic disease in Palestine is approximately similar to the occurrence of lichen planus in moderate climates, or even slightly less. In the series of cases referred to in this article, it occurred in approximately 0.2 per cent of patients with dermatologic disease. Silberstein[6] in Tel Aviv reported the incidence of lichen planus to be 0.14 per cent among 130,111 patients with dermatologic disease. Compared with percentages given by Spitzer[7] and Juliusberg,[8] the incidence we arrived at is slightly less than that in the United States, a survey of the American Medical Association, involving the years 1878 to 1911, giving an incidence of 0.442 per cent in a total of 676,376 patients with dermatologic disease. Similar percentages are found in Europe, for example, in England. From Copenhagen, Denmark, alone, an incidence as low as 0.1 per cent has been reported.

6. Silberstein, S.: Dermatological Physiognomy of Palestine, Harefuah **27**: 65-66 (Aug. 15) 1944.

7. Spitzer, R.: Geographische Verteilung der Hautkrankheiten, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 14, pt. 2, pp. 253-328.

8. Juliusberg, F.: Lichen ruber und Pityriasis rubra pilaris, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 7, pt. 2, pp. 1-221.

No data on the occurrence of lichen planus in tropical regions thus far are available. On the basis of our figures, lichen planus probably is of less frequent occurrence in tropical regions than in the majority of countries with a moderate climate.

Diagnosis.—So far as the localization and morphologic aspects of the disease are concerned, we observed, apart from the typical lesions as they are encountered all over the globe, a special variety of lesions of lichen planus. The usual lesions ordinarily develop preponderantly on the upper and lower extremities, the trunk, the mucous membranes and the genitals.[9]

The special type observed in Palestine—examples of which were presented at various meetings of the Dermatological Society in Jerusalem by Kaplan, Katzenellenbogen and one of us (Sagher)—preponderantly occurs on the exposed parts of the skin, and it is especially the forehead that is the site of predilection of these lesions. Occasionally, they are seen alone, but simultaneous involvement of the backs of the hands and the extensor aspects, particularly of the forearms, as well as the exposed parts of the chest and neck, is common. In Palestine the type seen is annular; there is a special inclination for the development of dark pigmentation in the center with a characteristically elevated edge of a bluish white tinge. This edge occasionally appears to have less pigment than the surrounding skin, which may be due to mechanical factors associated with the usually dark complexions of our patients. This is similarly the case with any infiltration. That is, the skin is stretched tautly over such infiltrated areas, so that there is a lesser quantity of pigment per square millimeter of skin. Consequently, the skin in such regions appears lighter than the surrounding parts. In 8 cases, involvement of the mucous membranes of the mouth was recorded, and in 4 cases, involvement of the genitals was noted. Diagnostically, the form and localization peculiar to the disease are interpreted correctly by the presence of typical nodules elsewhere on the skin, unless the forehead and the cheeks alone are involved, without typical primary efflorescences elsewhere. Difficulty in the diagnosis of lichen planus of the forehead was experienced in a number of examples presented at

9. (*a*) Juliusberg.[8] (*b*) Pautrier, L. M.: Le lichen plan; les lichénifications, in Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 7, pp. 435-564. (*c*) Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1945. (*d*) Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939. (*e*) Culver, G. D.: A Clinical Study of Lichen Planus, Arch. Dermat. & Syph. **1**: 43-49 (Jan.) 1920. (*f*) Jacob, F. M.: XVI. Some Studies on Lichen Planus Based on the Study of One Hundred and Seventy-Nine Cases, ibid. **2**:607-616 (Nov.) 1920.

dermatologic societies in Palestine.[10] Distinction between lichen planus of this type and lupus erythematosus hypertrophicus often appears to be difficult.[11] Similarly, distinction of this disease from poikiloderma[12] or Riehl's melanosis[13] is not easy.

We do not wish to conjecture as to whether, in the foregoing cases, the condition actually was lichen planus. We have mentioned them only to illustrate the difficulty that may be experienced when lichen planus is localized on the face alone. From the standpoint of differential diagnosis, ringworm, syphilis and annular types of seborrheic dermatitis must also be considered. The characteristically elevated bluish white edges of the lesions usually render diagnosis possible even in the absence of typical nodules elsewhere on the surface of the body. On the other hand, the clinical aspect of lichen planus with localization on the eyelids, such as was observed nine times among our patients, has been described comprehensively by Laymon[14] and Michelson and Laymon.[15]

10. (*a*) Abramowitz, E. W.: Pigmentary and Annular Lichen Planus Limited to the Face, Arch. Dermat. & Syph. **15**:491-492 (April) 1927; A Case for Diagnosis (Ephedrine Eruption? Lichen Planus?), ibid. **51**:160 (Feb.) 1945. (*b*) Fox, H.: Lichen Planus (?) Involving the Face, ibid. **5**:407 (March) 1922: in discussion on Combes.[10d] (*c*) Weise, E.: Lichen Planus Atrophicus, ibid. **27**:868 (May) 1933. (*d*) Combes, F. C.: Lichen Planus with Annular Lesions on the Face, ibid. **34**:523 (Sept.) 1936. (*e*) Becker, S. W., and Obermayer, M. E.: A Case for Diagnosis (Lichen Planus of the Eyelids?), ibid. **41**:1169-1170 (June) 1940. (*f*) Niles, H. D., in discussion on Costello, M. J.: Lichen Planus Atrophicus, ibid. **43**:737 (April) 1941. (*g*) Lane, C. G.: A Case for Diagnosis (Lichen Planus? Lupus Erythematosus?), ibid. **45**:415-416 (Feb.) 1942. (*h*) Rosen, I.: Lichen Planus and Fixed Drug Eruption? ibid. **46**:759 (Nov.) 1942. (*i*) Beerman, H., and McGuire, J.: A Case for Diagnosis, ibid. **49**:381 (May) 1944. (*j*) Freeman, H. E.: A Case for Diagnosis (Fixed Bismuth Dermatitis?), ibid. **52**:275 (Oct.) 1945. (*k*) Weissenbach, R. J., and Fernet, P.: Un cas de lichen plan atypique, Bull. Soc. franç. de dermat. et syph. **49**:310-311 (March) 1939. (*l*) Gougerot, H., and Blum, P.: Lichen plan pigmentogène cutanéo-muqueux atypique et typique, ibid. **45**:912-914 (June) 1938.

11. Duckworth, G.: Lichen sclerosus et atrophicus, Brit. J. Dermat. **56**:242-243 (Nov.-Dec.) 1944. Forman, L.: Lichen Planus, ibid. **57**:153 (July-Aug.) 1945. Civatte, A.; Tzanck, and Sidi: Lucite à forme de lupus érythèmateux subaigu: Traitement par la vitamine P. P., Bull. Soc. franç. de dermat. et syph. **46**:1344-1345 (Sept.-Oct.) 1939.

12. Gougerot, H., and Civatte, A.: Oscillations entre le lupus érythèmateux, le lichen plan, et la poïkilodermie: Discussion nosologique, Ann. de dermat. et syph. **3**:233-245 (Sept.-Oct.) 1943.

13. Degos, R.; Garnier, G., and Dobkevich: Pigmentations réticulées de la face (type mélanose de Riehl-poïkilodermie); Lichens planus, Bull. Soc. franç. de dermat. et syph. **50**:62 (Jan.) 1943. Storck, H.: Über Riehl'sche Melanose, Dermatologica **92**:246-258 (May-June) 1946.

14. Laymon, C. W.: Lichen Planus of the Eyelids, Arch. Dermat. & Syph. **36**:242 (July) 1937.

(Footnotes continued on next page)

Ordinary lichen planus, as a rule, occurs after the twentieth year of life and is evenly distributed throughout all age groups up to the age of 70 years. This has been pointed out by Culver[9e] and Jacob.[9f] The subtropical variety of lichen planus, however, is virtually absent among persons more than 50 years old, and it occurs only exceptionally among persons more than 40 years old. The youngest patient in our group who had subtropical lichen planus was 4 years old; 14 among the 51 in this group were less than 20 years old. This variety of lichen planus, therefore, appears to be confined to young persons.

Lichen Planus and Climate.—No mention of lichen planus usually is made in textbooks of tropical diseases. Fasal[16] reported that in Malaya lichen planus was in no way distinguished from lichen planus occurring elsewhere. Ambler[17] pointed out that in a number of soldiers the disease had become aggravated after the men had been transferred to tropical regions. He reported a number of cases in which hypertrophic lichen planus had involved large portions of the skin as well as the mucous membranes of the mouth and the lips. Whether, on the other hand, the symptoms similar to those of lichen planus observed after the use of quinacrine hydrochloride in New Guinea by Bagby,[18] Schmitt, Alpins and Chambers,[19] Nisbet[20] and Kierland,[21] and in Mediterranean territories by Nelson,[22] also were provoked by factors connected with the tropical or subtropical climate prevailing there, has not yet been decided. The fact, however, that lichen planus may run rather a dramatic course in tropical regions is illustrated by the cases described by Dowling.[23] In 2 soldiers who had come from Africa the onset was sudden, with a high tempera-

15. Michelson, H. E., and Laymon, C. W.: Lichen Planus of the Eyelids, Arch. Dermat. & Syph. **37**:27-29 (Jan.) 1938.

16. Fasal, P.: Cutaneous Diseases in the Tropics, Arch. Dermat. & Syph. **51**:163-171 (March) 1945.

17. Ambler, J. V.: Experience of a Dermatologist in the Southern Pacific, Arch. Dermat. & Syph. **49**:224 (March) 1944.

18. Bagby, J. W.: A Tropical Lichen Planus-Like Disease, Arch. Dermat. & Syph. **52**:1-5 (July) 1945.

19. Schmitt, C. L.; Alpins, O., and Chambers, G.: Clinical Investigation of a New Cutaneous Entity, Arch. Dermat. & Syph. **52**:226-238 (Oct.) 1945.

20. Nisbet, T. W.: A New Cutaneous Syndrome Occurring in New Guinea and Adjacent Islands, Arch. Dermat. & Syph. **52**:221-225 (Oct.) 1945.

21. Kierland, R. R.: Personal communication to the authors.

22. Nelson, L. M.: Unusual Dermatosis Simulating Lichen Planus and Lichen Corneus Hypertrophicus: Report of Six Cases, Arch. Dermat. & Syph. **55**:12-27 (Jan.) 1947.

23. Dowling, G. B.: (*a*) Two Cases of Lichen Planus, Brit. J. Dermat. **56**:245-247 (Nov.-Dec.) 1944; (*b*) Erythematous Lichen Planus, ibid. **56**:241 (Nov.-Dec.) 1944.

ture and loss of consciousness. The lesions were situated mainly on the face. Hellier,[24] in the discussion of these cases, pointed out that he had seen 2 patients, also coming from tropical regions, who had similar conditions. In these 2 patients, apart from hypertrophic lichen planus of the lower extremities, the ears, the neck and the region of the eyes and lips also were involved. Hellier thought of the possible effects exerted by sunlight or vitamin B deficiency. As far as can be concluded from the descriptions in the literature, the lichen planus in the cases referred to was different from the subtropical form of lichen planus we have described in our cases.

Lichen Planus and Sunlight.—Only few references are to be found concerning a possible connection between lichen planus and the rays of the sun. An adverse effect of sunlight on lichen planus already existing has been pointed out by Brunsting.[25] Niles[26] and Pautrier[27] described instances in which there were local recurrences after exposure to sunlight, although these studies, as well as the dissertation by von Engeln,[28] refer to minute nodules in the nature of an isomorphic irritation effect. Epstein and Jessner,[29] studying the problem of an isomorphic irritation effect in connection with lichen planus, reported on the development of local exacerbations after the administration of thorium, radium and roentgen rays. Local exacerbations did not, however, follow the use of ultraviolet rays, although the erythema produced by such rays was even more pronounced than that caused by the others. Epstein and Jessner expressed the belief that biologic differences in the nature of the rays applied probably play a decisive role. In Fellner's[30] case, too, lichen planus likewise was almost entirely confined to the exposed parts of the skin, but all the cases referred to thus far were cases of ordinary lichen planus, with its characteristic primary efflorescences.

A certain resemblance to the subtropical type of lichen planus, that we have described herein was reported by Verrotti[31] from Italy. He saw

24. Hellier, in discussion on Dowling.[23b]

25. Brunsting, L. A.: A Practical Skin Test for the Study of Photosensitivity: Discussion, Proc. Staff Meet., Mayo Clin. **16**:480 (July 23) 1941.

26. Niles, H. D.: Lichen Planus Atrophicus Annularis, Arch. Dermat. & Syph. **44**:1125 (Dec.) 1941.

27. Pautrier, L. M.: Dermite eczématiforme et lichen plan d'origine solaire, Bull. Soc. franç. de dermat. et syph. **38**:1393-1401 (Nov.) 1931.

28. von Engeln, H.: Ueber den isomorphen Reizeffekt beim Lichen ruber, Inaug. Dissert., Hamburg, Mediz. Fakultät, 1936.

29. Epstein, S., and Jessner, M.: Provokationsversuche bei Lichen ruber durch Strahlen, Arch. f. Dermat. u. Syph. **173**:311-316, 1935.

30. Fellner, M.: Zur Morphologie des Lichen ruber planus an der Gesichtshaut, Dermat. Wchnschr. **92**:1-6 (Jan. 3) 1931.

5 patients in whom the cutaneous manifestations developed at the exposed parts, such as the face and hands. He referred to the efflorescences, a description of which was accessible to us only in abstract, as being whitish achromic papules, with fine scaling. Casals[32] reported from Cuba that among 41 patients who had lichen planus, 73 per cent exhibited localization on the backs of the hands. There was, however, no difference in the condition as it appeared among white persons, mestizos and Negroes. In Casals' opinion, this effect of the sun would favor a parasitic causation of lichen planus in general; he expressed the belief that the disease represents actinodermatitis conditioned by phototropism.

Most of our patients came from southern regions or had been living in subtropical countries for a considerable length of time. Their complexions were definitely darker than those of persons from moderate zones. The appearance of the subtropical type of lichen planus on the exposed parts of the skin poses the question of whether it is the sunlight that is one of the responsible agents in the production of the disease. Such seems likelier to be true in view of the fact that in a number of patients recurrences were noted after exposure to the sun for some time; usually the recurrences are observed in the spring and summer.

Lichen Planus and Porphyrin.—The first determinations of porphyrin in the urine, made according to the method of Beckh, Ellinger and Spies,[1] yielded a few positive and a few doubtful results. However, since this method, in the opinion of Dobriner and Rhoads[3] as well as of Watson and Layne,[33] actually is not a determination of coproporphyrin in the urine, but rather of urorosein, these results were reassayed according to the method of Dobriner and Rhoads. This method produced values that were, throughout, less than the upper limits of normal excretion; that is, less than 100 micrograms of coproporphyrin were eliminated in the course of twenty-four hours. This is not particularly surprising, in view of the fact that the majority of photophobic diseases of the skin are not characterized by abnormal values for the excretion of coproporphyrin. Moreover, the special type of lichen planus concerned in our report involves relatively small areas of the skin. According to studies by Brunsting,

31. Verrotti, G.: Di una singolare varietà acromica di lichen nelle regioni scoperte, Gior. ital. di dermat. e sif. **66**(pt. 2):1173-1185 (Aug.) 1925; A Peculiar Variety of Achromic Lichen Planus, abstracted, Arch. Dermat. & Syph. **13**:249 (Feb.) 1926.

32. Casals, D. A.: Un caso de liquen plano de origen solar, Rev. de med. trop. y parasitol., bacteriol., clin. y lab. **10**:123-124 (Sept.-Dec.) 1944; El liquen de Wilson y su localización en el dorso de la mano, Rev. sif., leprol. y dermat. **3**:170-172 (Oct.) 1946.

33. Watson, C. J., and Layne, J. A.: Studies of Urinary Pigments in Pellagra and Other Pathological States: I. Clinical Observations, Ann. Int. Med. **19**:183-199 (Aug.) 1943.

Brugsch and O'Leary,[34] the usual sensitivity of the skin to light does not affect the excretion of porphyrin. For instance, in the presence of pellagra and lupus erythematosus an increased excretion of porphyrin could not be established. In the series reported by these authors, however, abnormal values for the excretion of porphyrin were observed in exfoliative dermatitis as a reaction to the use of neoarsphenamine—an observation that had been made, similarly, by Marquardt.[35] Even in xeroderma pigmentosum, McFarland and Strain[36] were able to establish normal values for the excretion of porphyrin, whereas, high values were observed in the presence of hydroa aestivale. The few reports of an increase in the excretion of porphyrin in various dermatoses characterized by sensitivity to light have referred to only a few cases; they are often doubtful, and, moreover, they have been refuted by other investigators.

In addition, results of all other examinations, such as tests of hepatic function and determinations of total protein and the production of erythema after ultraviolet irradiation in the affected and normal portions of skin, yielded nothing to indicate any pathologic mechanism that could be held responsible for the production of this special subtropical form of lichen planus.

The pathogenesis of the subtropical form of lichen planus must, therefore, be related to its outstanding clinical features, such as localization on the face and on the dorsal aspects of the extremities among pigmented persons, its morphologic characteristics and its seasonal fluctuation—all of them contributing to the picture of a photodermatosis. The analogy with pellagra is obvious, for pellagrous cutaneous manifestations also develop at the same time at the exposed and covered parts of the skin and have no special sensitivity to ultraviolet rays, but these pellagrous cutaneous manifestations nevertheless are considered to be photodermatosis. The special reaction to light is only one of the features of this type of avitaminosis. In the case of the special type of lichen planus that we have described herein, an unknown causative factor apparently is what sets in motion a mechanism that acts as a photodynamic force and is responsible for the morphologic features and localization peculiar to the condition.

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34. Brunsting, L. A.; Brugsch, J. T., and O'Leary, P. A.: Quantitative Investigation of Porpyhyrin Metabolism in Diseases of the Skin, Arch. Dermat. & Syph. **39**:294-307 (Feb.) 1939.

35. Marquardt: Porphyrinbestimmung im Urin und ihre Bedeutung bei Hauterkrankungen, Zentralbl. f. Haut- u. Geschlechtskr. **53**:525-526, 1936.

36. McFarland, A. R., and Strain, W. H.: Significance of Porphyrin Content of Urine in Dermatoses Associated with Sensitivity to Light, Arch. Dermat. & Syph. **38**:727-736 (Nov.) 1938.

SUMMARY

A special type of lichen planus has been observed among 51 patients. Probably it is confined to subtropical regions and is characterized by certain features, which are as follows:

Morphologically, the disease appears in an annular pattern, with pigmentation. It is confined mainly to the exposed parts of the skin, such as the face, especially the forehead, the extensor aspects of the upper extremities and especially the backs of the hands and forearms. This subtropical form of lichen planus has a special predilection for persons in the lower age groups. It occurs in persons of dark complexion coming from subtropical countries. Itching is almost entirely absent. The course of subtropical lichen planus is chronic; it extends over several years. The onset of subtropical lichen planus is distinctly seasonal; recurrences or spreading are likely to be observed in spring and summer and improvement, or even cure, in the rainy period. The response to treatment with grenz rays is comparatively good. It is supposed that a photodynamic factor determines the pathogenesis of the special type of lichen planus described herein.

ALOPECIA DUE TO METASTASES FROM ADENOCARCINOMA OF THE BREAST

Report of a Case

F. RONCHESE, M.D.
PROVIDENCE, R. I.

REPORT OF CASE

A 41 year old white woman, of Italian ancestry, had her right breast removed for adenocarcinoma on May 21, 1947. About six months later pea-sized nodules, with the pathologic characteristics of metastatic adenocarcinoma, developed around the surgical scar and on the face and back (fig. 1). Later the hair of the scalp began to fall out in spots, leaving irregularly round, smooth areas of alopecia, slightly and unevenly elevated, of the same color as the surrounding skin of the scalp (figs. 1*A* and 2). Metastases were also found on examination of the chest and bones. Biopsy of an alopecic and a hairy area of the scalp was done on Jan. 23, 1948. Examination showed a partially hairless, but otherwise normal, epidermis. The hairy part presented features of a normal hairy scalp. In the alopecic part of the corium the subcutaneous tissues were densely infiltrated by metastatic tumor cells, destroying and replacing the glandular and hairy structures (fig. 3).

The patient died on Jan. 25, 1948. Permission for autopsy was not obtained.

COMMENT

Most textbook classifications of noncicatricial, symptomatic or any other forms of alopecia do not include alopecia resembling the cicatrisata type which is due to metastatic carcinoma. As far as I know, only McCarthy[1] described localized areas of alopecia caused by pressure and ulceration from metastatic carcinoma or sarcoma.

The usual picture of neoplasm of the scalp, benign or malignant, local or metastatic, shows lack of hair on the tumor itself. In my previous case of metastases to the scalp,[2] the patient was an elderly man whose scalp was entirely covered with tumors. No particular attention was paid

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From the Tumor Clinic, Dr. B. E. Clarke, Director, and the Department of Dermatology, Rhode Island Hospital, Dr. F. Ronchese, Chief of Service.

1. McCarthy, L.: Diagnosis and Treatment of Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940, p. 601.

2. Ronchese, F.: Metastases of the Scalp Simulating Turban Tumors, Arch. Dermat. & Syph. **41**:639 (April) 1940.

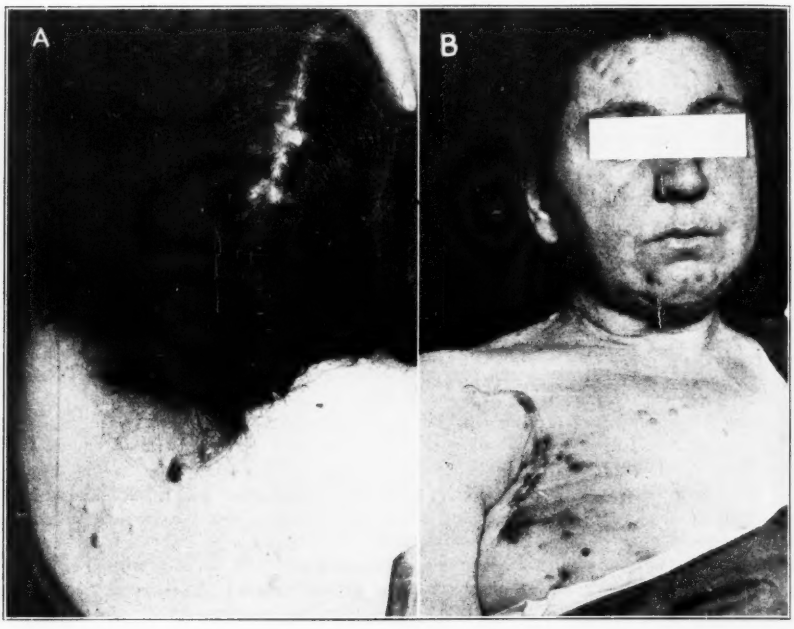

Fig. 1.—Metastatic nodules on scalp, back and chest from adenocarcinoma of the breast in a case of metastatic alopecia resembling alopecia cicatrisata.

Fig. 2.—Scalp of patient with alopecia resembling alopecia cicatrisata.

to the alopecia, which was considered an obvious sequela of the metastases and of the patient's age. Had this patient been seen with only spots of alopecia, before the stage of tumor formation, not much attention would have been paid to the condition, which would have been called alopecia areata or alopecia senilis. However, if I had been aware of the possibility of a metastatic alopecia, an early diagnosis of a malignant lesion elsewhere could have been considered.

In the present case, six weeks elapsed between the time when the loss of hair was noticed and the time when the appearance of the scalp was that illustrated in figures 1 and 2. If knowledge of the short dura-

Fig. 3.—Photomicrograph showing (*a*) normal scalp area and (*b*) hairless epidermis and infiltration of the corium and subcutaneous tissue by metastatic cells of adenocarcinoma, with destruction of the appendages of the skin; × 21.

tion of the alopecia, the history of a recently removed cancer of the breast and the presence of the nodular formations on the face, chest and back had been withheld from the examining physician, and he had been aware only of the loss of hair the tentative diagnosis could have been pseudopelade (alopecia cicatrisata).

A contributory factor to the uncertainty of the diagnosis is the absence of mention of metastatic alopecia from most textbooks of dermatology, and from textbooks of internal medicine and pathology (particularly those devoted to manifestations in the skin of internal diseases). Although uncommon or rare, such a condition is to be remembered in the differential diagnosis of noncicatricial, symptomatic alopecias.

SUMMARY

A case is reported of alopecia of the scalp resembling alopecia cicatrisata, from metastases of an adenocarcinoma of the breast.

Metastatic alopecia deserves mention among the noncicatricial, symptomatic alopecias.

Its recognition may help in the early diagnosis of an internal malignant tumor.

170 Waterman Street.

Clinical Notes

GRANULOMA PYOGENICUM GIGANTEUM

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LOS ANGELES

The history and microscopic appearance of tissue in the case described here were sufficiently typical to justify a diagnosis of granuloma pyogenicum, but the clinical appearance, especially the enormous size of the lesion, was so bizarre as to confuse the diagnosis.

Granuloma pyogenicum was first described under this name by Crocker[1] in 1903, although it had previously been reported by Poncet and Dor[2] in 1897 under the name botryomycose humaine. The first cases reported in the United States were described by Hartzell[3] in 1903. Since that time the disease has become a well established entity, familiar to all dermatologists.

Trauma is a common precipitating factor. The lesion may be present on any part of the cutaneous surface and in its common form occurs singly. It is usually pedunculated or sessile, is highly vascular, bleeds easily, with a moist or crusted surface, and attains the average the size of a pea, although lesions as large as a cherry have been described. The tumor may have a smooth surface, although it may show crevices filled with pus or have a frambesiform appearance. The lesions develop rapidly, but after attaining a certain size usually remain stationary and may persist for an indefinite period. The growth is considered in the nature of exuberant granulation tissue which has been infected with pyogenic bacteria, usually staphylococci, although other organisms have been reported.

Histologically the lesions are fairly characteristic, although there are variable features. Michelson[4] reviewed the clinical and histologic appearances in 29 cases of granuloma pyogenicum. He noted that the epidermal changes varied from erosion, with complete loss of epithelium, to extreme thickening, with hyperkeratosis and acanthosis. Sessile growths in particular often showed considerable lengthening of the rate pegs throughout the lesion, while the epithelium was often thinned or lost over the area between the pegs. Michelson stated that the amount of cellular infiltrate varied decidedly and also varied at different planes of the tumor, being greatest in the upper third, especially in eroded lesions and in

1. Crocker, H. R.: Diseases of the Skin, Philadelphia, P. Blakiston's Son & Co., 1903, vol. 2, p. 1081.

2. Poncet, A., and Dor, L.: De la botryomycose humaine: Identité de nature de tumeurs d'apparance papillomateuse chez l'homme avec la botryomycose ou champignon de castration du cheval, Lyon méd. **86**:213 (Dec.) 1897.

3. Hartzell, M. B.: Granuloma Pyogenicum (Botryomycosis of French Authors), J. Cutan. Dis. **22**:520-525 (Dec.) 1904.

4. Michelson, H. E.: Granuloma Pyogenicum: Clinical and Histological Review of Twenty-Nine Cases, Arch. Dermat. & Syph. **12**:492-505 (Oct.) 1925.

sessile tumors, where there was pronounced acanthosis. In lesions where the epithelium was intact, even though thinned, there was often complete absence of infiltrate. In certain specimens there was a line of demarcation between the infiltrate and the angiomatous portions of the tumor. Michelson observed that the infiltrate was leukocytic, with various types of cells, round cells and polymorphonuclear leukocytes predominating. Mast cells were observed, and free red blood corpuscles were often present. Michelson did not observe giant cells, although he

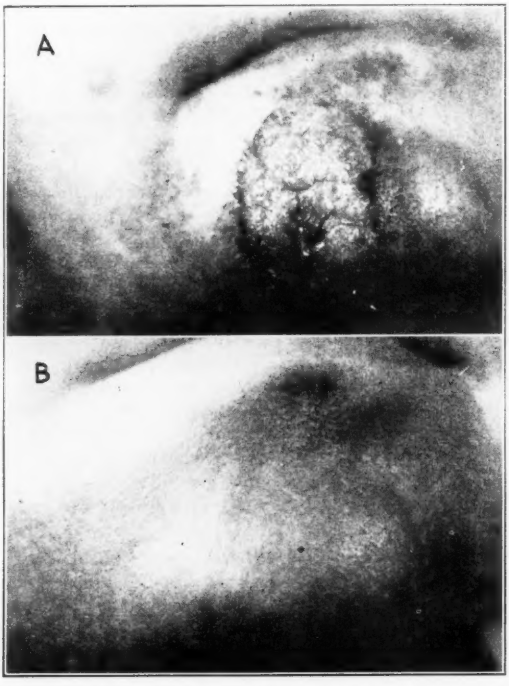

Fig. 1.—*A*, granuloma pyogenicum of giant size following trauma. *B*, appearance four weeks after removal of growth by curettage and cauterization with silver nitrate.

stated that Kreibich recorded observing them. Michelson did not mention plasma cells, although Wile,[5] in an earlier comprehensive review of the subject, stated that "the plasma cell content of the tumors was in no case sufficiently striking to attract marked attention, although present to a degree in all cases."

Michelson, in agreement with other observers, found the new blood vessel formation to be constant, varying only in the number and size of blood vessels or blood spaces. In certain specimens the vessels were small and all of the same size; in others the size varied a great deal, large dilated lacunas being packed with red

5. Wile, U. J.: Granuloma Pyogenicum, J. Cutan. Dis. **28**:663-674 (Dec.) 1910.

blood cells. The vessels and spaces all had thin endothelial linings. In some specimens the angiomatous area was diffuse; in others it occurred as a distinct zone. The spaces between the blood vessels were occupied by connective tissue, cellular infiltrate or mucoid substance.

REPORT OF A CASE

L. P. M., a white man aged 38, a sheepherder, was referred for examination of a lesion on the chin.

According to the history, the lesion had been present for only eight days and had developed a few days after the patient had been butted on the chin by a ram. Previous treatment had consisted of three injections of penicillin of unknown quantity, given ninety minutes apart one week previously, and the local application of wet boric acid compresses. The lesion had not improved. The patient had not been aware of any fever.

Examination revealed a tumor on the right side of the chin, measuring approximately 3 by 3.5 cm. and covering nearly the entire right half of the chin. The lesion was elevated, boggy, erythematous and covered with a yellowish crust. Removal of the crust revealed a lobulated appearance, with deep crevices and a cobblestone-like surface. The growth was attached by a broad base. Few hairs were seen except in the crevices. There was a thin, seropurulent exudate.

Two weeks elapsed betwen the first and the second visit, during which time the patient received elsewhere an undetermined amount of sulfadiazine by mouth, penicillin by injection and two roentgen ray treatments, without appreciable change in the appearance of the lesion except that there was less crusting.

Laboratory Observations.—Direct examination of the seropurulent exudate macerated with 40 per cent potassium hydroxide failed to reveal any fungi. The Gram stain showed many staphylococci. Dark field examination revealed no spirochetes. Culture on Sabouraud's medium yielded no growth. Cultures on plain agar showed Staphylococcus aureus. Reactions to the Kahn and Kline tests were negative.

Histologic Examination.—In places the epidermis was thinned; in others there was pronounced hypertrophy with greatly elongated rete pegs. The corium was largely made up of loose, newly formed connective tissues and enlarged capillaries and vascular spaces. There was a pronounced infiltrate, consisting chiefly of small round cells, polymorphonuclear leukocytes and a few plasma cells and eosinophils. In portions of the section, apparently of more recent development, the epidermis showed pronounced parakeratosis; the upper portion of the corium was largely empty of cellular elements, apparently being filled with edema fluid and fibrin, into which new budding capillaries and fibroblasts were sprouting. Elsewhere, the cellular infiltrate, capillaries and new connective tissue were fairly dense through out. In places free red cells were observed in the tissue spaces.

Treatment and Subsequent Course.—With the use of procaine anesthesia, the entire mass was removed with a sharp curet. The tumor tissue was friable and was easily scraped away, leaving a raw, bleeding base. As the overlying growth was removed, the normal hairs of the chin came into view, as though they had been buried by a lava flow. The bleeding was stopped by pressure and by the application of a 25 per cent solution of silver nitrate. The patient was seen at two or three day intervals through the ensuing week, during which subsequent applications of 25 per cent silver nitrate were made and wet packs of alibour water (water containing zinc and copper sulfate) diluted 1:8 were used between visits.

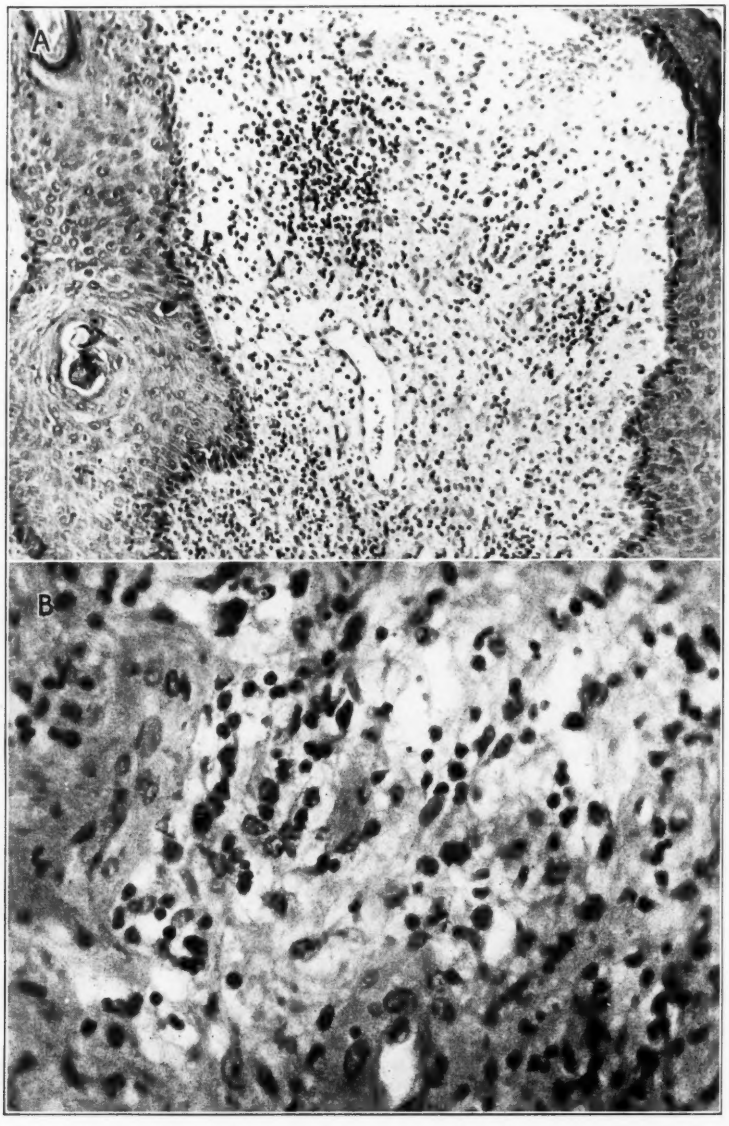

Fig. 2.—*A*, photomicrograph showing hypertrophy of rete pegs, newly formed connective tissue, vascular spaces and infiltrate. *B*, higher power photomicrograph showing character of infiltrate.

The wound healed rapidly, and four weeks after the operation the chin appeared normal, with no evidence of scarring and with normal growth of beard.

COMMENT

It is felt that the case reported here fulfils all the requirements for a diagnosis of granuloma pyogenicum: rapid onset and development after trauma, ultimate attainment of a size which remained stationary, the clinical appearance of a sharply localized, fibrovascular, encrusted tumor with seropurulent exudate, typical histologic features and total disappearance after superficially destructive procedures.

The unusual size of the lesion, giving rise to such a bizarre appearance as to offer a diagnostic problem, is nearly unique in the literature on the subject. According to recent available authorities, the size of the lesion of granuloma pyogenicum varies from that of a pea to that of a cherry. Sutton and Sutton[6] cited a questionable case, in which the lesion, measuring 5 cm. in diameter, involved the right cheek. Michelson referred to a case, presented by Armstrong[7] before the Minnesota Dermatological Society, of a lesion "as large as a small hen's egg"; but a check on the reference cited by Michelson showed that Armstrong had described the lesion in his case as being "nearly an inch (2.5 cm.) in length," or considerably smaller than a hen's egg. In all probability, lesions as large as or larger than the one presented in this paper have been observed, but they must be extremely rare.

The diagnosis of the average pea-sized lesion usually offers no problem, but when the lesions are large various other diagnostic possibilities are called to mind, such as a malignant neoplasm, a deep fungous infection or chancre. A diagnosis of chancre was certainly entertained in this case and was the reason for dark field examinations. Michelson stated that a flat, sessile lesion may look surprisingly like a chancre, and he mentioned a case in which it required negative results in dark field examinations on three successive days to convince himself and a colleague that they were not dealing with a chancre. According to Michelson, a diagnosis of granuloma pyogenicum should include all sharply circumscribed granulation tissue growths occurring on cutaneous or mucous surfaces and having the appearance of a tumor. In his experience, the average diameter of the lesions is 1 cm.

This criterion would include such conditions as epulis granulomatosa, described by Thoma,[8] and granuloma fissuratum, originally described by Sutton and Sutton.[9] Both these neoplasms are composed of fibrovascular, tumor-like masses, the former occurring on the gum and usually arising from an infected tooth socket, the latter occurring in the alveololabial sulcus, usually as the result of friction from a loose denture.

Michelson also emphasized that pedunculation is not requisite for diagnosis. Many lesions are attached by a broad base.

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6. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 941.

7. Armstrong, J.: Granuloma Pyogenicum, Arch. Dermat. & Syph. **2**:128 (July) 1920.

8. Thoma, K. H.: Clinical Pathology of the Jaws with a Histologic and Roentgen Study of Practical Cases, Springfield, Ill., Charles C Thomas, Publisher, 1934, pp. 344-391.

9. Sutton and Sutton,[6] pp. 1486-1487.

SUMMARY

An unusual case of granuloma pyogenicum of giant size which followed trauma to the chin is described. The lesion was destroyed without scarring by means of curettage, followed by cauterization with 25 per cent silver nitrate.

2007 Wilshire Boulevard.

CONTACT DERMATITIS DUE TO PHENOLPHTHALEIN

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Since Abramowitz'1 initial report suggesting phenolphthalein as a cause of certain cutaneous eruptions, many cases of dermatitis medicamentosa have been described due to ingestion of this drug. The following unusual case of dermatitis due to contact with phenolphthalein is reported in the belief that it is the first authentic case of its kind to be described.

REPORT OF A CASE

J. R., a 28 year old white soldier, was admitted to the station hospital at Fort Mead, Md., in March 1944, with nasopharyngitis. He received the usual routine care and an occasional back rub with the hospital alcohol. About one week after admission he was referred to the dermatology clinic because of an eruption which suddenly appeared on his entire back. The history revealed that he had had a back rub with the hospital alcohol the day before, and no other obvious causative factors were elicited. Examination showed a severe erythematovesicular eruption covering the entire back. Investigation of the alcohol compound revealed that it contained a trace of tincture of cudbear, added only as a coloring agent, and 1 grain of white phenolphthalein powder to the ounce of 70 per cent ethyl alcohol. The latter agent had been added to the alcohol by the hospital pharmacy in an attempt to discourage use of it for beverage purposes by ward personnel. The patient was instructed to return the next day for a patch test, and when he did so there was a patch of erythematovesicular dermatitis in the left cubital fossa where this same alcohol mixture had been applied prior to a venipuncture. Patch tests were performed on the flexor surface of the right forearm with the alcohol mixture, plain 70 per cent alcohol, alcoholic and aqueous solution of tincture of cudbear, 0.2 per cent alcoholic and aqueous solutions of white phenolphthalein and with the dry phenolphthalein powder. In twelve hours there was a bullous reaction to the original alcohol compound used for rubbing and to the other testing materials containing phenolphthalein. No reaction was noted at the site of tests with materials not containing phenolphthalein. The eruption subsided in several days, and the patient was warned of his intolerance to the local use of phenolphthalein. Since the patient was otherwise ready for duty, a trial dose of phenolphthalein was not given orally.

SUMMARY

A proved case of contact dermatitis due to phenolphthalein is reported since this undoubtedly is an extremely infrequent cause of contact dermatitis.

1000 Asturia Avenue.

*Formerly a captain in the Medical Corps, Army of The United States.

1. Abramowitz, E. W.: Erythema Multiforme Associated with Cutaneous Pigmentation (Melanin), J. Cutan. Dis. **36**:11, 1918.

USE OF CARBOXYMETHYLCELLULOSE IN LOTIONS

EUGENE S. BERESTON, M.D.
BALTIMORE

Jansen[1] first developed carboxymethylcellulose in Germany in 1918 as a substitute for gelatin, glue, agar-agar, tragacanth and similar substances. Carboxymethylcellulose is used chiefly in industry in the form of its sodium salt. Sodium carboxymethylcellulose is indicated whenever hydrophilic colloids having suspending, stabilizing, film-forming and thickening properties are needed.

Brown and Houghton[2] stated that sodium carboxymethylcellulose can be used as an emulsifying agent and whenever a protective colloid is required in oil in water emulsions. According to these authors, it is nontoxic.

About a year ago I became interested in the possibility of using carboxymethylcellulose in dermatology, particularly in lotions when oil in water emulsions are needed. After many trials, I compounded a lotion consisting of the following formula in aqueous solution: sodium carboxymethylcellulose, 0.75 per cent; nonaethylene glycol monolaurate, 1 per cent, and triethanolamine, 1 per cent.[1a] In this formula the carboxymethylcellulose acts as a film-forming agent and stabilizes the emulsion. The nonaethylene glycol monolaurate was included because it emulsifies liquid petrolatum, while the triethanolamine was added to emulsify the fixed oils, such as olive oil. The lotion thus compounded is greaseless, odorless, colorless and film forming. It adheres well to the skin. It may be employed as a vehicle for all types of drugs used in dermatology, for it is compatible with oils, solids and liquids except for the soluble salts of zinc and aluminum; this means that Burow's solution (solution of aluminum acetate N. F.) cannot be incorporated with it.

The lotion is easily removed from the skin with water. Patch tests on several hundred people gave no positive reactions; in clinical use in the past year and in private practice no contact dermatitis from its use has been seen. It forms an addition to the therapeutic armamentarium of the dermatologist.

CONCLUSION

A lotion containing carboxymethylcellulose has been studied and observed to be greaseless, colorless, odorless, film-forming, nontoxic and nonsensitizing and has been found to be a suitable vehicle for the administration of common dermatologic drugs.

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1. Jansen, cited by Hollabaugh, C. B.; Burt, L. H., and Walsh, A. P.: Indust. & Engin. Chem. (Indust. Ed.) **37**:943, 1945.

1a. Material was furnished by the Castill Drug Company, Baltimore.

2. Brown, C. J., and Houghton, A. A.: J. Soc. Chem. Indust. **10**:254, 1941.

ALOPECIA AREATA ASSOCIATED WITH REFRACTIVE ERRORS

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and
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Although alopecia areata has been known for many years as a distinct clinical entity offering little difficulty in differential diagnosis, the cause remains unknown, as evidenced by the many case reports suggesting different theories of causation.

Typical alopecia areata may appear at any age, in either sex, and may involve the scalp, eyebrows or bearded region. It usually occurs with a sudden asymptomatic loss of hair, leaving a sharply circumscribed oval or irregular smooth noninflammatory area of almost complete alopecia, containing only a few so-called exclamation point hairs. In rare instances the alopecia may become total. In differential diagnosis, syphilitic "moth-eaten" alopecia, ringworm of the scalp, trichotillomania, folliculitis decalvans, lupus erythematosus, scars and radiation alopecia must be considered, as well as acute local infectious processes.

A patient with the usual case of alopecia areata, with or without treatment, ordinarily shows regrowth of hair in a period of three to six months, but in middle-aged or elderly patients the regrowth is likely to be white. At times new areas of alopecia continue to appear during regrowth in areas of previous disease. There is no specific treatment for the disease.

The literature contains many articles suggesting various causes of alopecia areata and cites cases which have appeared in association with numerous conditions. Templeton and his co-workers[1] reported alopecia areata after local exposure to ethyl gasoline. Several cases associated with dental infections have been reported by Grace,[2] Jacquet[3] and others. Bergman[4] reported alopecia areata resulting from injections of quinine dihydrochloride and urethane. Joseph[5] in 1886 produced spots of alopecia, analogous to alopecia areata, by sectioning the occipital nerves of cats, although Auburn[6] was unable experimentally to repeat these results. Hubble and Rogerson[7] wrote, " . . . It has not been difficult . . . to demon-

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1. Templeton, H. J.; Michael, G., and Key, J. M.: Epilating Action of Ethyl Gasoline, Arch. Dermat. & Syph. **37**:35-42 (Jan.) 1938.

2. Grace, J. D.: Extensive Alopecia Areata of Dental Origin, Arch. Dermat. & Syph. **45**:349-352 (Feb.) 1942.

3. Jacquet, L.: Sur la nature et le traitement de la pelade: La pelade d'origine dentaire, Ann. de dermat. et syph. **3**:97-129, 1902.

4. Bregman, A.: Alopecia Areata Artificially Produced by Intravenous Injection of Quinine Hydrochloride and Ethyl Carbamate (Urethane), Arch. Dermat. & Syph. **35**:285-286 (Feb.) 1937.

5. Joseph, M.: Experimentelle Untersuchungen über die Aetiologie der Alopecia areata, Monatsh. f. prakt. Dermat. **5**:483-489, 1886.

6. Aubrun, E. A.: Pruritus and Hyperesthesia Caused by Partial Sensory Denervation: Experimental Alopecia—Contribution to Study of Alopecia Areata, Arch. Dermat. & Syph. **34**:564-567 (Oct.) 1936.

7. Hubble, D., and Rogerson, C. H.: Anxiety; Alopecia Areata; Neurofibromatosis; Auricular Fibrillation, Brit. M. J. **1**:486-488, 1944.

strate a preceding emotional stress." No statistics were cited. Sabauraud[8] observed that in 11 cases out of 100 the tendency toward the disease was inherited. Bowen[9] and several other writers have reported what they considered to be epidemics of alopecia areata.

As for normal observations, Strickler and Greenberg[10] in a series of 30 cases observed that 91 per cent of the roentgenograms of the sella turcica were normal, excluding pituitary disturbance as a cause. Waisman and Kepler[11] were unable to disclose any gross clinical evidence of constant functional endocrine abnormality in a series of 138 cases of alopecia areata.

The theory of peripheral reflex nervous irritation as a cause of alopecia areata was first mentioned by Jacquet[3] in 1902. Jacquet was unable to support any theory of epidemics, nor was he able to observe any parasitic agent. He did observe that in many cases the disease was associated with foci of dental irritation, such as dental caries, erupting third molars and apical abscesses, as well as sinusitis. This theory was later broadened to include the irritation caused by refractive errors. The first cases of alopecia areata associated with refractive errors that we were able to find were reported by Whitfield[12] in 1904 and Kingsbury[13] in 1909, who suggested that possibly the presence of eye strain might be of causative significance. Little has subsequently been added concerning the relation of errors of refraction to alopecia areata.

We became interested in this relationship about ten years prior to the date of writing, and refraction was subsequently done for all willing patients. This possible causative factor was mentioned in a previous article by one of us (H. A. H.) in 1942.[14]

During the past ten years 163 patients with alopecia areata have been seen by one of us (H. A. H.), and refraction has been done by various ophthalmologists, with a constant observation of errors of refraction. In 61 of the patients the refraction was done by one of us (T. L. P.). Accordingly, the discussion of the errors will be limited to these 61 patients, as it was felt that a constant check by a single ophthalmologist would be more uniform. Of these 61 patients with alopecia areata, 26 were male and 35 female. The only patient seen in the first decade of life was a boy aged 4 years. There were 2 women aged 64 and 66, respectively, who were the only patients seen above the age of 51 years. The rest of the group varied between the ages 11 and 51, with the majority falling in the age group be-

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8. Sabauraud, R.: Nouvelles recherches sur l'étiologie de la pelade, Ann. de dermat. et syph. **2**:65-71, 1911.

9. Bowen, J. T.: Two Epidemics of Alopecia Areata in an Asylum for Girls, J. Cutan. & Genito-Urin. Dis. **17**:399-404, 1899.

10. Strickler, A., and Greenberg, S. I.: Alopecia Areata: Roentgen Studies of Sella Turcica, Arch. Dermat. & Syph. **37**:1008-1009 (June) 1938.

11. Waisman, M., and Kepler, E. J.: Alopecia Areata: An Appraisal of Endocrine Factors in Its Causation, J.A.M.A. **116**:2004-2006 (May 3) 1941.

12. Whitfield, A.: A Contribution Towards the Etiology of Alopecia Areata, Lancet **1**:651, 1904.

13. Kingsbury, J.: Three Cases of Alopecia Areata Associated with Ametropia, J. Cutan. Dis. **27**:211, 1909.

14. Haynes, H. A., Jr.: Alopecia Areata, Ohio State M. J. **38**:1116-1117, 1942.

tween 20 and 40 years. All patients were given the same local medication, to be used twice weekly—a shampoo of 10 per cent resorcinol in liniment of soft soap and the following lotion to be rubbed on the scalp after shampooing and rinsing:

	Gm. or Cc.
℞ Solution of coal tar	24
Castor oil	6
Oil of clove	6
Methyl salicylate	6
Alcohol (95%), in sufficient quantity to make	240

These prescriptions were used, not because they were felt to be of value but to help satisfy the patients that "something was being done."

All refractions for the 61 patients with alopecia areata revealed errors for which glasses were prescribed. Normal visual acuity without correction does not rule out an error of refraction, as 44 patients or 72 per cent had 20/20 uncorrected vision. Ninety-five per cent of these patients had astigmatism, and in all but 3 of them, the amount was under 1 D. Seventy-three per cent of the patients with astigmatims had an oblique axis. In a survey of two hundred routine refractions in office practice, 85 per cent revealed astigmatism, and 50 per cent of these (or 42.5 per cent of all cases) revealed an oblique axis. While the percentage of astigmatism at an oblique axis is definitely higher in the group with alopecia areata, it does not in any way follow that astigmatism at an oblique axis must be associated with alopecia areata. The only possible association we can presume is that an oblique axis might cause more reflex nervous irritation. Muscular imbalance of any appreciable amount occurred in only 5 per cent of the patients with alopecia areata and therefore appeared to be of no significance. Twenty-five of the 61 patients had been wearing glasses previously, and a change of lenses was indicated in all of them.

Observations of Refractions in 61 Patients with Alopecia Areata Examined Between the Years of 1938 and 1947.

Observation	No. of Patients
Astigmatism	59
Myopic or compound myopic astigmatism	16
Hyperopic or compound hyperopic astigmatism	35
Mixed astigmatism	4
Myopic astigmatism in one eye; hyperopic astigmatism in the other	4
Presbyopia	13
Muscular imbalance	3

It is important that the glasses be worn continuously, as shown by results in a male patient aged 19. This patient, who had had regrowth of hair with no recurrence in three years, had a recurrence January 1946, after he had ceased to wear his glasses because of a cutaneous irritation of his ears and nose. Refraction showed no change in his error, and the spectacle frame was changed from the plastic to the gold type. Regrowth again occurred in about three months. It is also important to keep the correction up to date, as shown by results in a man aged 48, who had had regrowth following the wearing of his first glasses but had a recurrence two years later. Recheck of his lenses showed a change in the astigmatic axis and the onset of presbyopia. Regrowth occurred following the change in the prescription.

Twenty-two, or 36 per cent, of the patients were examined between the years of 1938 and 1943. Regrowth followed the wearing of glasses in approximately three months, without recurrence. The remainder of the patients have been examined since December 1945, and of these, there was failure of regrowth in 2.

SUMMARY

Refraction was performed for 61 patients wih alopecia areata, and all were observed to have errors, the predominant one being a small astigmatic error at an oblique axis.

In general, there was a rapid regrowth of hair in three months following the continuous wearing of glasses, with no recurrence as long as the error was adequately corrected.

We do not assume that refractive errors are the sole cause of alopecia areata, but such a constantly high percentage of relationship suggests that reflex nervous irritation from the refractive error may possibly be a cause.

A refraction is indicated in all cases of alopecia areata, and the continuous wearing of glasses with an adequate correction is recommended.

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FAMILIAL MULTIPLE NEVI FLAMMEI

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Although vascular nevi are generally considered to be inherited,[1] pedigrees do no seem to have been published. Actually, the genetic background has been essentially derived from the study of the occurrence of these nevi in twins.[2] In particular, nevus flammeus has but rarely been reported to have been inherited. Siemens[3] and Cockayne,[4] in their comprehensive surveys on heredity in cutaneous diseases, cited but a single known instance in which nevus flammeus appeared in parent and child. Their reference was to Benedict,[5] who described a family in

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From the Department of Dermatology and Syphilology, Hospital of the University of Pennsylvania, Philadelphia, Dr. Donald M. Pillsbury, Director.

1. Gates, R. R.: Human Genetics, New York, The Macmillan Company, 1946, vol. 1, p. 294.

2. Meirowsky, E.: Moles and Malformations of the Skin in Their Relationship to Inheritance and Phylogenesis (New and Old Investigations), Brit. J. Dermat. **54**:99, 1942.

3. Siemens, H. W.: Die Vererbung in der Aetiologie der Hautkrankheiten, in Jadassohn, J.: Die Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, vol. 3, pt. 1.

4. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, Oxford University Press, 1933.

5. Benedict, H.: Heredodegeneration und postdiphtherische Lähmung, Deutsche Ztschr. f. Nervenh. **46**:492, 1913.

which the mother had a large discontinuous portwine stain on the right side, involving the chest, arm and shoulder, while 1 of her 5 children presented a large portwine stain covering the right side of the chest and neck and the right arm. Strangely, even though nevus flammeus of the nape of the neck is seen in 5 per cent of the population,[6] published pedigrees of the occurrence of this type of nevus flammeus are also lacking.

Recently we have had occasion to study multiple nevi flammei in a brother and a sister, whose pedigree revealed a striking familial occurrence of multiple birthmarks reported to be identical in appearance to their own.

REPORT OF CASES

CASE 1.—Patient J.O.B. was a 24 year old unmarried white female secretary, who stated that she had always had numerous birthmarks. Her past medical history included tonsillectomy in 1926, appendectomy in 1942, bacillary dysentery in 1945, and acne vulgaris about 1943-1946. Her general state of health had been good. Her family history revealed that 12 of 28 members of her family (four generations) had similar "birthmarks" on various areas of their skin. Physical examination revealed the presence of moderate acne vulgaris of the face, an angiomatous purplish submucosal mass on the right side of the lower gum, a small café au lait spot over the dorsum of the left foot and the dark red patches on the skin subsequently described. The skin presented ten dark red nonelevated sharply circumscribed irregular angular patches, varying in size from 0.5 by 0.7 cm. to 3.5 by 4.5 cm. They showed definite fading on diascopic examination, leaving a residual brownish hyperpigmentation. The subcutaneous tissue gave a barely perceptible doughy sensation when grasped between the fingers. The defects were distributed on the thenar eminence of the right hand, anterior surface of the right upper arm, volar surface of the left forearm, left shoulder, left half of the posterior surface of the chest (3 lesions), posterior surface of the right leg, posterior surface of the right thigh and medial surface of the left knee. General physical examination revealed no other abnormalities.

A biopsy of the lesion on the thigh was made, and histologic study[7] showed a moderate increase in the number of capillaries present. A Bodian stain revealed no abnormalities of nerve tissue. A diagnosis of nevus flammeus was made.

CASE 2.—Patient J.I.B., the 16 year old brother of patient J.O.B., had multiple birthmarks. His general state of health had always been good. His presenting complaint was acne vulgaris of the face, which had been present for three years. In 1943 he had an appendectomy and a herniorrhaphy on the right side. General physical examination revealed nothing abnormal except the cutaneous lesions. In addition to moderately severe acne vulgaris of the face, he exhibited ten dark red, sharply circumscribed, irregular, angular and asymptomatic patches, varying in size from 0.1 by 0.2 cm. to 5 by 8 cm. These patches showed definite fading on diascopic examination, leaving residual brownish hyperpigmentation. Nine of the ten lesions were nonelevated, whereas the tenth, which was the largest lesion, was overlying a soft doughy tumor, which was said to fluctuate in size periodically. The lesions were distributed on the left elbow, posterior surface of the left upper arm (4 lesions), left scapular region, left upper quadrant of the abdomen, left

6. Corson, E. F.: Nevus Flammeus Nuchæ: Its Occurrence and Abnormalities, Am. J. M. Sc. **187**:121, 1934.

7. Report of Dr. Herman Beerman.

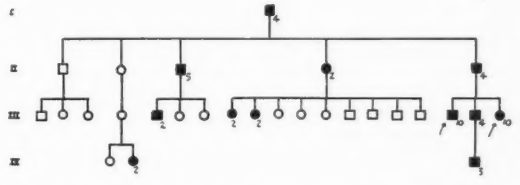
knee, calf of the right leg, right knee and medial aspect of the right leg. A clinical diagnosis of multiple nevi flammei was made.

The chart presents the pedigree as reported by the patients after they had questioned their relatives. Unfortunately, observations could be made on only the 2 siblings, and, as a result, the pedigree may be assumed to report some "false negatives."

COMMENT

Genetically this familial occurrence suggests an irregular dominant pattern of inheritance. The high frequency of occurrence (in 12 of 28 members) tends to rule out a recessive trait in a family not exhibiting consanguineous marriages. The nevi apparently did not occur in two consecutive generations and reappeared, unless it is assumed that members II_2 and III_4 (standard labeling) had small nevi which escaped notice. Accordingly, the pattern is an irregular one. However, no rigid genetic conclusions can be made in the absence of a complete examination of each member of the family.

It is of interest that pedigrees of patients with multiple nevi pigmentosi have been published,[4] showing that the inheritance of these involves a simple dominant



Pedigree of a sibship in which multiple nevi flammei appeared in certain members. This was drawn according to the report of the propositi (➤). The number of nevi is indicated at the lower right of the affected person's symbol. The squares and circles represent male and female members, respectively.

trait. The claim was made that these nevi may be a form fruste of hereditary neurofibromatosis,[8] even though histologic studies give no supporting evidence.[9] In patient J.O.B., a single café au lait spot was the solitary observation bearing any relation to such an inherited abnormality. Others in the sibship may have an occasional pigmented nevus, but the typical mark was described as a reddish patch, which has been assumed by us to be nevus flammeus.

CONCLUSION

Multiple nevi flammei in a brother and a sister are described, and a four generation pedigree is presented which suggests the nevi to be genetically determined on the basis of an irregular dominant trait.

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8. Cockayne.[4] Thannhauser, S. J.: Neurofibromatosis (von Recklinghausen) and Osteitis Fibrosa Cystica Localisata et Disseminata (von Recklinghausen): Study of Common Pathogenesis of Both Diseases, Medicine **23**:105, 1944.

9. McNairy, D. J., and Montgomery, H.: Cutaneous Tumors of von Recklinghausen's Disease (Neurofibromatosis), Arch. Dermat. & Syph. **51**:384 (June) 1945.

KERATOSIS FOLLICULARIS WITH CHANGES IN THE SKIN, MUCOUS MEMBRANE AND NAILS

Report of a Case

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We recently observed a case of keratosis follicularis with changes in the oral mucosa and finger nails in addition to the usual cutaneous changes. A review of the current literature shows that such a combination is not common. Ormsby and Montgomery[1] mentioned that nails show subungual hyperkeratosis and changes in the nail plate, and they referred to Reenstierna,[2] who described lesions on the tongue. Sutton and Sutton[3] referred to Brünauer[4] and Frost[5]; Frost described the occurrence on the gums, at the level of the bicuspids and molars and extending to the hard palate, of minute, whitish papules, which give a rough sensation to the touch.

Our patient was a woman aged 20, who worked in a printing office wrapping paper. She had noticed her dermatologic disorder for five years and stated the belief that the spongy, hypertrophic gums had been present since the advent of her permanent teeth. At times, the gums bled when the teeth were cleaned; the nails had been easily broken and had split at the distal margins for about four years.

The abnormality of the skin was made up of small, firm, reddish papules, which had been discrete at times but had become confluent, especially in the supraclavicular and infraclavicular regions and in the hair line on the anterior temporal region on both sides. These papules were greasy to the touch. There were a few papules, more nearly the normal color of the skin, around the nasolabial folds. On removal of some of the crusted, confluent papules in the clavicular region, a red, follicular, enlarged opening was seen. The gum of the anterior portion of the upper jaw was hypertrophic to such an extent as to interfere with speech. This hypertrophy was red and spongy to the touch. There was no pain on pressure, and the gums of the lower jaw and the posterior portion of the upper jaw were normal. There were no lesions elsewhere in the mouth. The finger nails were thin and longitudinally ridged and were broken irregularly and split longitudinally at the distal margins, with characteristic changes.

From the Department of Dermatology, Loyola University School of Medicine.

1. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, pp. 508-512.

2. Reenstierna, J.: Dariersche Dermatose mit Schleimhautveränderungen und impetigoartigen Eruptionen, Arch. f. Dermat. u. Syph. **124**:841, 1918.

3. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 9, St. Louis, C. V. Mosby Company, 1935, pp. 592-597.

4. Brünauer, S. R.: Ueber Schleimhautveränderungen bei Morbus Darier and über die Pathogenese dieser Erkrankung, Acta dermat.-venereol. **6**:131, 1925.

5. Frost, K.: Dyskeratosis Follicularis (Darier's Disease), Arch. Dermat. & Syph. **31**:508 (April) 1935.

Histologic examination of a portion of skin removed from the clavicular region and stained with hematoxylin and eosion showed acanthosis and disruption, irregular in outline, of the basal layers. There were round bodies in regions of dyskeratosis and grains in the adjacent areas of parakeratosis. These changes took place in the region of the opening of sebaceous glands on the skin.

At the time of this report, the patient has been under treatment for four months, with considerable improvement. She has taken 200,000 units of vitamin A daily for twenty days and has received several grenz ray exposures, as Wise[6] suggested. The involved skin has become smooth, and the single lesions have disappeared. The hypertrophic gums have receded, and the patient states they no longer bleed when brushed. The finger nails do not split as they formerly did. Instead of the hard, oily, seemingly crusted skin of the clavicular regions, the area is smoother and nonscaly. Residual brown pigmentation is present.

SUMMARY

A case of keratosis follicularis is reported because of the unusual changes in the mucous membrane and in the finger nails, as well as the usual changes in the skin.

Vitamin A therapy produced a pronounced amelioration in the size of the cutaneous lesions. Grenz rays were also used and believed to have been of benefit.

706 South Wolcott Street.

6. Wise, F., in discussion on Bechet, P. E.: Darier's Disease Associated with Possible Diabetes Mellitus, Arch. Dermat. & Syph. **35**:1205 (June) 1937.

REACTIONS TO SODIUM BISMUTH TRIGLYCOLLAMATE ("BISTRIMATE")

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Recently there was a report[1] on the efficiency of sodium bismuth triglycollamate tablets ("bistrimate tablets," Carroll Dunham Smith Pharmacal Company) for the treatment of lupus erythematosus and other chronic dermatoses.

To date the only report of untoward reactions from use of the drug which has come to our attention is that made by Gross,[2] of temporary gastrointestinal disturbances, with anorexia, nausea and vomiting. During the past months we treated 2 patients, 1 of whom had gastric disturbance in addition to oral lesions, and the other an entirely different series of reactions involving the skin and mucous membranes, following ingestion of "bistrimate."

1. Sulzberger, M. B.: 1945 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1946, p. 31.

2. Gross, E. R., in discussion on Wright, C., and Gross, E. R.: Disseminated Lupus Erythematosus Treated with Sodium Bismuth Triglycollamate ("Bistrimate Tablets"), Arch. Dermat. & Syph. **55**:862 (June) 1947.

REPORT OF CASES

CASE 1.—M. E., a white woman aged 42, presented lesions of typical discoid lupus erythematosus, of three and one-half years' duration, involving the cavum conchae of the auricles and the postauricular areas, extending down the sides of the neck and up onto the cheeks. Her previous treatment consisted of several courses of treatment with gold sodium thiosulfate, but no therapeutic benefit was observed. We treated her at various times with intramuscular injections of bismuth subsalicylate, extract of liver and vitamin B complex. Nicotinamide tablets were taken orally. Solid carbon dioxide was applied at times to the infiltrated individual lesions. Phenyl salicylate and tannic acid ointment and lotion were prescribed for topical application. The lesions receded slightly, but remarkable progress was not made. We then prescribed "bistrimate." The patient was instructed to take 1 tablet four times daily the first week and then 2 tablets three times daily. On the sixteenth day of medication a severe headache developed in the back of the neck, extending up to the frontal area; there was soreness of the skin of the face; the eyes became puffy and swollen, and ringing in the ears was troublesome. The gums became swollen and began to bleed, interfering with mastication and hygiene, and, in addition, a bluish line on the gums was observed. The symptoms were present for three days before she reported to us. We ordered the medication to be discontinued. The reaction continued to be intense for about a week and subsided entirely in about a month. Observations of the urine and the blood were normal.

CASE 2.—A. W., a white woman aged 26, had had lupus erythematosus for three years. At first treatment with nicotinamide and vitamin B complex was effective in clearing the eruption. In January 1947, there was a recurrence on the forehead, cheeks and chest. This time repetition of the same treatment was not effective. We prescribed "bistrimate." Four tablets were taken on the first day and 2 on the next. Vesicles appeared on the buccal mucous membrane of the mouth and on the tip of the tongue the first day and became worse as the tablets were continued on the second day. In addition, soreness developed in the abdomen. There were no other symptoms—no nausea and no vomiting—just soreness. The patient discontinued the medication. Soreness of the abdomen continued for another day, and the vesicles subsided after several days. Observations of the urine and the blood were normal.

SUMMARY AND CONCLUSIONS

The use of sodium bismuth triglycollamate ("bistrimate") in 2 patients was accompanied with reactions which necessitated the discontinuance of treatment with the drug. The reactions consisted of pain in the head, swelling of the eyelids, soreness of the skin of the face, swelling and bleeding of the gums, bluish discoloration of the gums and tinnitus, in the first case. There were vesicles of the tongue and mouth and soreness of the abdomen in the second case. Medication was not continued long enough in either case to alter the appearance of the cutaneous lesions, and we did not attempt to prescribe the medicine again in either case.

814 Equitable Building.

Society Transactions

NEW YORK DERMATOLOGICAL SOCIETY

Eugene F. Traub, M.D., *President*
George M. Lewis, M.D., *Secretary*

Oct. 22, 1946

A Case for Diagnosis (Radiodermatitis? Psoriasis? Dermatitis Venenata?). Presented by Dr. Howard Fox.

Lichen Planus Annularis et Hypertrophicus in a Child. Presented by Dr. Maurice J. Costello.

Melanoma. Presented by Dr. Eugene F. Traub.

F. S., a girl aged 10, received an injection for whooping cough at the age of about 1 year. The mother stated that the needle punctured a pigmented nevus on the right arm. Shortly thereafter, the mother noticed a number of small coffee-colored pigmented areas that had appeared within a diameter of 2 to 3 inches (about 5 to 7.5 cm.) around the original site. Several of the pigmented areas became inflamed and slightly nodular. At the present time there is a group of variously sized pigmented lesions, some elevated and some flat, several of which have slightly red and inflamed areolas. None of the pigmented lesions measures more than 2 cm. in its greatest diameter. None of the marks resemble the pigmented nodules usually seen in the skin at or around the site of a malignant melanoma and representing metastasis from such a lesion. There has been no treatment to date.

One of the small slightly elevated nodules, with some redness about the periphery, was removed, and the section was studied by Dr. Barthel. The epidermis was relatively normal, with pigment in the basal cell layer. The corium was filled with strands and masses of pale-staining cells as well as dark brown pigment. Occasional small islands were present, such as are seen in a melanocarcinoma.

DISCUSSION

Dr. Paul E. Bechet: It is surprising to note the occasional low grade of malignancy in melanomas occurring in children. A notable example and a duplicate of the disease in Dr. Traub's patient occurred in a girl of 14 or 15 years who was treated in my clinic at the New York Skin and Cancer Hospital prior to 1934. Around the right eye and involving the lids was a deep black melanotic lesion about 70 mm. in diameter, with satellite lesions. The girl was in good health, and the lesions had been present since she was a few months old, a fact corroborated by Dr. Cole of Cleveland, who had seen the patient at that age. This confirmed the fact that a large nodular deeply pigmented lesion has been present for the entire life of the 15 year old patient, without change and without any effect on her general health. The case does not serve as a criterion for non-intervention in lesions of this type, and it would be dangerous to make such a deduction, but it does prove that a few lesions of this kind apparently have a benign course.

DR. FRED WISE: My impression is that the lesion is relatively benign and that treatment should be conservative. I doubt that the injection had anything to do with the present lesions.

DR. GEORGE M. MACKEE: It is impossible for anyone to say whether or not the puncture had anything to do with the activity. Both clinically and histologically it looks like an early nevocarcinoma arising in a junction nevus. Lesions of this type do not respond well to radiation. I suggest a wide deep excision and plastic repair.

DR. HOWARD FOX: I agree with Dr. Wise. I believe that treatment should be conservative, and I doubt that it is melanocarcinoma.

DR. MAURICE J. COSTELLO: I agree with Dr. Fox and Dr. Wise.

DR. J. GARDNER HOPKINS: It is an interesting example of the relatively benign character of melanocarcinomas or melanomas in young children, but I do not believe that it is absolutely benign. There is a melanotic growth that has already disseminated in the region. It seems to me that the only safe procedure is to remove all involved tissue. It may not affect the outcome, but it is the only prudent course.

DR. GERALD F. MACHACEK: I reiterate what Dr. Hopkins said: Malignant melanomas are somewhat less malignant during childhood than in adult life. If it is going to be treated at all, a wide excision should be performed.

DR. RAY H. RULISON: I feel that if this entire lesion is widely excised, the child will not be greatly harmed and there is a chance that it might obviate later trouble. If the child dies with generalized melanomatosis, somebody will be bitter.

DR. JOHN C. GRAHAM: I would excise the area and perform a plastic operation.

DR. GEORGE M. LEWIS: I am in favor of active surgical intervention.

DR. EUGENE F. TRAUB: I brought up the point regarding the injection given this patient at or about the site of the original pigmented nevus because of the belief that in some instances malignant melanomas have originated from puncture wounds. Naturally this is difficult to prove in a given instance, but in this case there is a straightforward history of the development of most of the pigmented marks following the puncture, so that it must be given due consideration. Nevertheless, it is my opinion that this is just a nevus that is developing with the child and that portions of it were simply delayed in appearance, a rather common occurrence in persons with this type of nevus. Another point I wish to emphasize is that Dr. Barthel reported that the lesion of which she made a biopsy was a malignant melanoma. The lesion for removal was selected at random, and the supposition is that some or all of the other lesions are malignant melanomas or that they are all junction nevi. It is more likely that they are junction nevi, as the lesions do not appear to be metastatic and it is hardly to be expected that ten or more lesions would originate as malignant melanomas. A similar case was presented before this society by Dr. Cannon about a year ago. A number of lesions were removed, and all were reported to be malignant melanomas. They were probably all junction nevi, because, if I recall correctly, none of the physicians thought them particularly malignant. I do not believe that the lesions in this patient are particularly malignant; nevertheless, because the pigmented lesions are all relatively closely grouped in one large patch, it would probably be wiser and safer to remove the entire area and cover the site with a skin graft.

A Case for Diagnosis (Guttate Scleroderma in Zosteriform Distribution?). Presented by DR. MAURICE J. COSTELLO.

A. T., a woman aged 48, has an eruption involving the region of the right shoulder and the upper half of the right arm in zosteriform distribution, which has been present for about six months.

The eruption consists of discrete irregular, hard, nonpainful, lentil-sized to pea-sized nodules, which can be more readily palpated than seen, although they are visible plainly under the Wood light as dusky purplish nodules. These infiltrated nodules can be better observed when seen from an angle.

Other than mild secondary anemia, the patient is well. She has a moderately enlarged cystic thyroid gland.

DISCUSSION

DR. HOWARD FOX: I don't see how one could make a definite clinical diagnosis of scleroderma or Schweninger-Buzzi type of macular atrophy at present. I think that a biopsy is required to settle the question.

DR. FRED WISE: I agree with the presenter's diagnosis.

DR. PAUL E. BECHET: The lesions are raised, with a suggestion of atrophy but no sclerodermatous changes. While there is no patulence, an early type of Schweninger-Buzzi disease might be considered. However, it is not possible to make a diagnosis on the basis of one short inspection, though it might well be that time will prove the correctness of the tentative diagnosis.

DR. GERALD F. MACHACEK: This is another case in which the diagnosis must be substantiated by biopsy.

A Case for Diagnosis (Schamberg's Disease? Disseminated Angiomata? Nevus Tardus?). Presented by DR. GARDNER HOPKINS.

K. M., a school boy aged 16, is presented with a purpuric eruption of one year's duration. About one year ago a purpuric spot appeared on the right shin and has persisted. In the past three months, twenty or more similar lesions have appeared on each thigh and leg, about six more appeared on the right forearm and a few minute ones occurred on the left forearm. There have been no subjective sensations. The patient is robust and apparently in good health.

The original plaque is almost rectangular, measures 3 by 4 cm. and is a uniform deep dusky red except in the line of a scar which crosses it and which is white. There is no infiltration, and no epidermal change is seen. Other lesions are smaller round plaques or macules, and a few are made up of branching linear streaks. Individual 1 mm. dull red vessels can be seen in some lesions, but no typical cayenne pepper points and no yellow staining.

Biopsy showed purpura with hemorrhage and pronounced lymphocytic infiltration around vessels in the papillary layer of the corium.

The clinical picture, with no change in the lesions for several months, seems incompatible with purpura, and the report of biopsy is incompatible with hemangioma.

Sarcoid (Boeck) with Solid Edema of the Eyelids Resembling Lupus Erythematosus. Presented by DR. MAURICE J. COSTELLO.

A Case for Diagnosis: Seborrheic Dermatitis (Benign Pemphigus? Erythema Multiforme?). Presented by DR. RAY H. RULISON.

DISCUSSION

DR. JOHN C. GRAHAM: I thought that the lesion, clinically, looked more like angioma. I think of the lesion in Schamberg's disease as being macular. These lesions were raised, and there was no atrophy, as in Majocchi's disease.

DR. GERALD F. MACHACEK: There are three possibilities: Schamberg's disease, Majocchi's disease and lichenoid purpuric dermatitis of Blum. Having seen the patient and the section, I would be inclined to diagnose the disease as Majocchi's disease, although the histologic picture was not characteristic.

DR. RAY H. RULISON: It does not conform with my impression of Schamberg's disease. Highmay claimed that Schamberg recanted and said that there was no such disease, and I have never seen the disease in a patient.

DR. FRED WISE: I would exclude Schamberg's disease, because that is progressive pigmentary dermatosis and there is no pigment visible in the eruption in this patient.

DR. GEORGE M. MACKEE: I think that it is early Majocchi's purpura annularis telangiectodes.

DR. HOWARD FOX: I think that Dr. MacKee is right, and he has made a special study of this type of eruption. I also think that Dr. Wise is right in saying that it could not possibly be Schamberg's disease. I am still waiting to have somebody show me a real case of the latter disease, with differentiation from hypostatic pigmentation.

DR. PAUL E. BECHET: I have seen many cases presented as cases of Schamberg's progressive pigmentary dermatosis which were clinically indistinguishable from dermatitis hemostatica, so that I strongly suspect that Schamberg's disease is not a dermatologic entity but the result of stasis from poor circulation. It should probably be classified as dermatitis hemostatica, which is as good a name as can be found for the somewhat varied clinical manifestations of cutaneous extravasation of blood which follow varices or stasis in the lower extremities.

DR. EUGENE F. TRAUB: The textbook descriptions of Schamberg's disease and Majocchi's disease make it difficult at times for one to understand the exact clinical differences between these two eruptions. In some books they are even referred to as possible variants of one and the same disease. Dr. Schamberg, while in New York, saw a patient whom I presented before this society with the questionable diagnosis of Schamberg's disease, and he, too expressed the opinion that so little was known about these entities that a clinical diagnosis was difficult to make. In this instance, the most probable diagnosis seems to be Majocchi's disease.

Cutaneous and Osseous Xanthomatosis, Complicating Congenital Atresia of the Bile Ducts, and Biliary Cirrhosis. Presented by DR. GERALD F. MACHACEK.

Recurrent Painful Fissue of the Vermilion Border of the Lower Lip in a Trumpeter. Presented by DR. MAURICE J. COSTELLO.

A Case for Diagnosis (Nonspecific Granuloma? Blastomycosis?). Presented by DR. JOHN C. GRAHAM.

Panniculitis in a Patient with Diabetes. Presented by DR. GERALD F. MACHACEK.

E. K., a woman aged 66, is presented from the Vanderbilt Clinic with a generalized eruption of four months' duration. Subcutaneous lumps first began to appear on the right forearm, left scapular region and right hip and have since

become generalized except on the face. They are firm and slightly tender and range in size from 1 to 5 cm. A few lumps are moderately inflamed, and some are attached to the skin. In the left breast in the upper medial quadrant, there is a tumor about 5 cm. in diameter, in the lower lateral quadrant there are two smaller tumors, and one in the lower medial quadrant is attached to the skin. There is no enlargement of the axillary lymph nodes. Two tumors were excised from the abdomen for microscopic examination. With the exception of one tumor on the left arm, the development of which followed an injection of ragweed allergenic extract, none of the masses occurred at the site of injections.

There is a scar from a thyroidectomy at the base of the neck. No cervical glands are palpable. Slight kyphosis is present. The skin of the ankles is atrophic, and no pulsation of the dorsalis pedis arteries can be felt.

The patient had scarlet fever as a child, typhoid at the age of 20 and diphtheria at 35. At the age of 15 an abscess developed at the base of the spine, which was drained on four occasions, the last time at the age of 31. Twenty-six years ago, at the age of 40, a hysterectomy was performed for a tumor of the neck of the womb, and this was followed by the menopause. Twenty years ago she suffered from hyperthyroidism, and thyroidectomy was performed. She has had pneumonia and attacks of biliary colic. A daughter died at the age of 20 of pneumonia, and a son is living and well at the age of 40.

Five years ago, after she had pruritis vulvae, it was discovered that the patient had diabetes. She lost about 24 pounds (about 11 Kg.) at that time. She has taken insulin for five years—35 units of protamine zinc insulin at first, which was decreased to 20 units, and on occasion she has received ordinary insulin. The tumors did not appear at the site of injection of insulin. About three months before admission, five fatty tumors and inflammatory masses were removed, but new ones developed. Five months ago the patient weighed 145 pounds (about 66 Kg.). Her admission weight was 140 (about 63.5 Kg.). She has received allergenic extract for hay fever and has taken injections of hormone preparations for five years. She was given a sulfonamide drug three years ago.

Laboratory tests revealed the blood sugar to be 152 mg. and cholesterol 211 mg. per hundred cubic centimeters. The Rh factor was positive, and the blood group was A. The Kline reaction of the blood was negative. The results of the glucose tolerance test are listed in the table.

Results of the Glucose Tolerance Test

Time	Blood Sugar, Mg./100Cc.	Urinary Reduction
Fasting	123 mg.	—
½ hr.	203 mg.	—
1 hr.	233 mg.	—
2 hr.	270 mg.	++
3 hr.	303 mg.	+++

Roentgenologic examination disclosed no metastases in the lungs or bones, but a large group of gallstones was noted in the right upper quadrant of the gallbladder. Atrophic changes of the colon appeared to support the history of colitis since birth.

Histologic examination disclosed an inflammatory reaction and necrosis involving primarily the subcutaneous fat as well as the corium, with mural thickening and proliferation of the larger vessels.

DISCUSSION

DR. J. GARDNER HOPKINS: Dr. Machacek has shown us 1 of 2 cases of similar disease, which apparently represents a clinical entity distinct from other recognized forms of panniculitis.

DR. FRED WISE: What is the prognosis?

DR. THOMAS N. GRAHAM: The lesions in this patient are almost identical to those I saw in a patient at New York Hospital. Dr. Lewis probably recalls the patient. She, too, had had no attacks of fever, but she did not have diabetes.

DR. GERALD F. MACHACEK: I cannot answer the question as to prognosis categorically, because I have observed the disease to be variable. In the first case I saw, the lesion healed after incision. The individual lesions heal spontaneously, and new ones develop. I have been able to follow up these cases long enough to know what the prognosis is when the diabetes is controlled. (Since the case was presented, localized cutaneous gangrene has developed in lesions at points of pressure on the ankle and the thigh.)

Amyloidosis Cutis of the Legs, Chest and Forearms. Presented by DR. FRED WISE.

Mycosis Fungoides Beginning with Poikilodermatous Cutaneous Lesions. Presented by DR. EUGENE F. TRAUB.

Pemphigus Erythematosus and Erythroplasia of the Penis. Presented by DR. GERALD F. MACHACEK.

J. W. W., a man aged 72, is presented from Vanderbilt Clinic with a generalized eruption of one year's duration. The patient was admitted on March 22, 1944, at which time he was suffering from hematuria due to a papilloma of the urinary bladder, which was subsequently removed. Benign prostatic hypertrophy and balanoposthitis were present. The glans penis was reddened, slightly thickened and indurated. A patch of leukoplakia was present near the frenum. Circumcision was performed, and the lesion of the penis was excised. About a year ago, numerous small blisters occurred on the sternum. These ruptured promptly, and the lesions spread to the arms, back and abdomen. The patient denied taking drugs and stated that itching is slight.

Scattered on the trunk and arms are numerous large erythematous areas, varying from 1.5 to 3 cm. in diameter. There are also lesions on the face, some of them on the cheeks and bridge of the nose. The lesions are in various stages of vesicular and bullous formation. Some are intact, and others are covered with a thick dirty gray crust. Nikolsky's sign was positive.

The patient appeared to improve with treatment with sulfapyridine, 0.5 Gm. four times a day.

Biopsy of the cutaneous lesions disclosed minimal changes, predominantly in the epidermis. Individual epithelial cells tended to be somewhat swollen and rounded. The changes were consistent with the diagnosis of pemphigus erythematosus.

Examination of tissue removed from the penis showed an intramucosal epithelioma of the nature of Bowen's disease. From the sections of the tumor of the urinary bladder, a diagnosis of epithelioma of a papillary type was made.

DISCUSSION

DR. MAURICE J. COSTELLO: I wonder whether Dr. Lewis, in discussing this case, would say whether he thought that the disease in this patient resembled the disease in the patient with chronic benign familial pemphigus (Hailey-Hailey disease) that he presented at a recent dermatologic meeting. The patient I refer to also had lesions in the mouth. I think that the lesion on the penis began as part of the generalized eruption on the body. I do not believe that two dermatoses were present from the onset.

Dr. George M. MacKee: I agree with the diagnosis as presented, but I also thought along the same lines as Dr. Costello. The only thing seen to suggest erythroplasia dyskeratosis is the penile lesion. If dyskeratosis can be observed in some of the lesions of the body, it would be Hailey-Hailey pemphigus.

Dr. Fred Wise: I am inclined to agree with Dr. Costello and Dr. Mackee in regard to Hailey-Hailey pemphigus.

Dr. George M. Lewis: I understand that the biopsy specimen from the penis showed a definite epithelioma, and, if so, that lesion must be different from the lesions present elsewhere.

Dr. Gerald F. Machacek: I considered the possibility of benign chronic (Hailey-Hailey) pemphigus, but I do not believe that the amount of dyskeratosis and the amount of vesiculation, from a histologic point of view, were sufficient for making that diagnosis. I considered the material excised from the penis carefully. What one sees now on the glans penis is what remained after operation, circumcision and thorough destruction. Originally leukoplakia and a definite tumor existed, and I think that the diagnosis of neoplasm is correct. It was an intramucosal epithelioma (erythroplasia).

Dr Maurice J. Costello: Did the lesion on the penis antedate the generalized eruption?

Dr. Gerald F. Machacek: It did. The patient has had the generalized eruption for about a year. The penile lesion was present when the patient was admitted to the clinic March 22. There was temporary improvement of the generalized eruption following the administration of sulfapyridine.

Granuloma Annulare (Necrobiosis Lipoidica Diabeticorum?). Presented by Dr. Fred Wise.

A Case for Diagnosis (Lymphoblastoma? Mycosis Fungoides?). Presented by Dr. Fred Wise.

H. H., a man aged 27, registered at the Skin and Cancer Unit on Aug. 6, 1946, presenting lesions of seven months' duration. He had measles, mumps and whooping cough as a child. He gave a history of taking "alka-seltzer" (a mixture of acetylsalicylic acid with sodium bicarbonate and citric acid) and "bromo-seltzer" (each dose contains 0.16 to 0.23 Gm. of acetanilid and 0.32 to 0.45 Gm. of sodium bromide) once in about six weeks and "ex-lax" (phenolphthalein in chocolate base) occasionally. He gave no history of allergy. His general health has been good.

In May 1946, itching began in the cubital fossae. A week later, red itchy areas appeared on the face and neck. Similar red blotches appeared a week or two later, in succession, on the shoulders, trunk and extremities; these gradually enlarged. On July 1, bald spots appeared on the scalp. The patient had occasional chilly sensations even in warm weather. The lesions have never regressed.

The entire integument except that of the hands and feet is involved. The lesions consist of well defined slightly raised discrete and confluent erythematous patches, which are covered with fine crusting and scaling. They are painless, are not tender and are somewhat rough to touch. They are slightly to moderately infiltrated. They vary from dime sized to palm sized to large diffused areas, some of which are on the left shoulder, lower part of the back, buttocks and sides down to the middle of the thighs, where they form networks enclosing normal-appearing skin. There are irregular fairly well marginated patchy areas of alopecia, most pronounced on the vertex and on the back of the scalp: some of these areas are covered with scale. The outer lateral half of the left eyebrow, the axillas and the

pubic areas also have patches of alopecia. The lymph nodes in the axillas are pea sized to cherry sized, with a shotty feel. The left epitrochlear node is enlarged. The lymph nodes in the groins are discrete and confluent, ranging in size from that of a pea to less than that of a cherry. They are all painless. Diascopic pressure does not cause fading of the lesions.

The results of routine laboratory tests were normal. The erythrocyte sedimentation rate was 21 mm. per hour (normal 10 mm. per hour, by the Westergren method). Sternal puncture was attempted, but a dry tap was obtained. Direct examination and culture of the scrapings of the patchy areas of the scalp did not reveal tinea.

Four biopsy specimens were taken from various lesions and studied by Dr. Charles F. Sims. The diagnosis on biopsy of the specimen taken August 13 was "exudative discoid and lichenoid chronic dermatosis (Sulzberger-Garbe)." The epidermis was somewhat irregular, with rather elongated and broadened rete pegs. In some places hypergranulosis could be seen, and in others there was thinning of the granular layer. The vessels of the upper part of the corium were moderately dilated and surrounded by a mild cellular reaction, composed for the most part of plasma cells. Concerning the biopsy specimen taken on September 19, "observations were of early changes suggestive of lymphoblastoma." The epidermis was somewhat irregular, with elongated rete pegs and some areas of parakeratosis. At some points intercellular edema could be observed and some exostosis. In the upper and middle layers of the corium there were pronounced reactions, some perivascular and others diffuse. The reaction was polymorphous, composed of small round wandering connective tissue cells and plasma cells. There were some rather pyknotic nuclei and some cells which were difficult to classify. The diagnosis on biopsy of an axillary lymph node was "chronic lymphadenitis of the axillary lymph nodes" (Dr. R. Lattes of the New York Post-Graduate Hospital). There were large collections of reticuloendothelial cells and brown granular pigment.

DISCUSSION

Dr. George M. Lewis: The lesions of the scalp would suggest alopecia areata, but some of the other lesions present are more suggestive of parapsoriasis, although the intensity of the reaction seemed too great for that.

Dr. Paul E. Bechet: The clinical picture is that of unusually scaly parapsoriasis of the chronic, resistant and scaly erythrodermatous type. Whether mycosis fungoides will develop presents the usual problem. The scaling on the scalp is caused by the same dermatosis, even though it suggests an eczematoid type of seborrheic dermatitis.

Dr. George M. MacKee: I suspected one of the lymphoblastomas.

Dr. J. Gardner Hopkins: Does parapsoriasis ever cause loss of hair? That seems to me a possible clue. Diseases which do cause loss of hair are eruptions due to "atabrine" (quinacrine hydrochloride) or other drugs, lupus erythematosus, which the disease in this patient does not resemble, and lymphoblastoma.

Dr. Eugene F. Traub: I would also like to hear something further about Dr. Hopkins' question. It has always been my opinion that parapsoriasis practically never was observed on the scalp or the face and that it never caused loss of hair.

Dr. Fred Wise: I have not heard that parapsoriasis caused loss of hair. This patient has a history of remissions and exacerbations, some of them occurring as little as one day apart. He would be better one day, for example, and then suddenly there would develop an erythematous eruption with itching, which is against the diagnosis of parapsoriasis.

MANHATTAN DERMATOLOGIC SOCIETY

David Bloom, M.D., *President*
Wilbert Sachs, M.D., *Secretary*
New York, Nov. 12, 1946

Xanthoma Juvenile (Nevoxanthoendothelioma, Solitary Lesion on the Forehead). Presented by DR. DAVID BLOOM.

A Case for Diagnosis (Tuberculosis Cutis? Syphilis? Acute Rosacea?). Presented by DR. FRED WISE.

L.M.C., a single woman aged 51, a patient of Dr. Maurice Husik, presents lesions on the nose of more than six weeks' duration. She had chickenpox as a child. In 1936 an operation on the gallbladder, an appendectomy and a right inguinal herniotomy were performed. The patient has otherwise been in good health. She denies having had any venereal infection.

The eruption began with a lesion resembling herpes simplex on the left side of the upper lip. This lesion healed, and a similar one appeared above it. About three weeks prior to presentation, a "little rash" appeared on the alae nasi simultaneously, and then the lower half of the nose gradually became involved.

The patient presents edema of the lower two thirds of the nose, which is almost twice the normal size. There are ill defined pea-sized rounded nodular lesions on each side of the alae nasi, which are coalesced and joined at the bases. On the left side there is one pea-sized similar nodule, which is isolated. There are a few small depressed scarred lesions on the right side of the upper lip. The lesions are painless. On diascopic pressure the nodules are easily compressed, revealing whitish patches.

The Wassermann reaction of the blood was negative.

DISCUSSION

DR. HERMAN SHARLIT: I saw the patient at the clinic this afternoon, and my impression was that the disease is syphilis, in spite of the negative Wassermann reaction.

DR. MAX SCHEER: My impression is also one of syphilis.

DR. WILBERT SACHS: The rapidity of development made me think of an eruption due to one of the halogens.

DR. ISADORE ROSEN: I agree with those who believe that this is a tertiary syphilitic infiltration. The question of rosacea and tuberculosis can be ruled out when one studies the features presented by this patient. The involved area is made up of a patch which is irregular in outline, consisting of small brownish red nodules which strongly suggest tertiary syphilis.

DR. MAURICE J. COSTELLO: I think that the patient has some form of tuberculosis, possibly sarcoid. There is too much infiltration, and the lesions have almost a waxy appearance. I do not base this on the negative Wassermann reaction, but on the clinical appearance. However, I do not believe that a person with tertiary syphilis in this location would have a negative Wassermann reaction.

DR. THOMAS N. GRAHAM: The eruption impressed me as being probably lupus vulgaris or a tuberculid. That the eruption is bilateral is against tertiary syphilis. The negative serologic reaction also makes a diagnosis of tertiary syphilis improbable. I think that one seldom sees a tertiary syphilid without a positive Wassermann reaction.

DR. GEORGE C. ANDREWS: The disease is difficult to diagnose in this case, and I am not sure of the diagnosis. The duration of six weeks and certain other clinical features strongly suggest syphilis. However, the history indicates that the eruption began with vesicles, and the serologic reaction is negative. The duration is short for sarcoid.

DR. DAVID BLOOM: If I had to make a diagnosis, I would favor sarcoid. The eruption resembles the lesions seen on the alae nasi or on the ear lobes in disseminated hematogenous tuberculosis in the Negro. However, six weeks is too short a period for a tuberculous lesion to develop.

Disseminated Sarcoid with Ulcerated Lesions. Presented by DR. ISADORE ROSEN. **Scrofuloderma.** Presented by DR. FRED WISE.

M. I., a man aged 59, registered at the Skin and Cancer Unit on Sept. 24, 1946, presenting cutaneous lesions of two years' duration. He had diphtheria at the age of 5. The patient stated that "diabetes" was observed on routine examination of the urine at 20 years of age. He has had cataract of the right eye since 1911. During the past two years "tuberculous glands" developed on the front of the chest, on the neck and in the axillas. Except for the lesions under the arms, they did not rupture. He has had three operations under general anesthesia during the past two years.

When the patient was first seen on October 8, there were many oozing lesions in the axillas, on the front of the chest and on the neck. On November 8 there were numerous irregular raised scars and two pea-sized ulcerated oozing lesions in the left axilla. In the right axilla was a 7 by 5 cm. irregular erythematous patch, with scars and sinuses from which purulent fluid oozed. There was a similar large pea-sized ulcer on the right of the sternum, just below the level of the third rib. There were thinned scarred areas on the right clavicle and irregular scarring along the entire base of the left side of the neck. A walnut-sized cold abscess was located in the left submaxillary region; this was incised and the serum injected into a guinea pig. On the upper part of the left side of the chest was an irregular flattened plaque of 2 cm., from which a biopsy specimen was taken. There was an irregular subcutaneous walnut-sized mass at the base of the right axilla, the skin of which was slightly erythematous and adherent. There was also a large irregular lymph node on the left posterior cervical region, which was adherent to the underlying structures and over which the skin was freely movable. There were palpable epitrochlear lymph nodes and an irregular cherry-sized lymph node at the base of the right posterior cervical region.

The urine was normal. The Wassermann and Kahn reactions of the blood were negative. Broth culture of the fluid aspirated from the cold abscess on the left side of the neck showed Staphylococcus albus. A roentgenogram of the chest showed "moderate pulmonary emphysema (postatrophic type) toward the bases."

Biopsy of the raised plaque on the left side of the chest was made by Dr. Charles F. Sims, and the diagnosis was tuberculosis cutis. The epidermis was somewhat irregular, with occasional spots of parakeratosis. Throughout the middle and deep layers of the corium was a rather massive cellular reaction, composed of what appeared to be epithelioid cells and scattered giant cells, with numerous small round wandering connective tissue cells. Many dilated and congested vessels were noted. The picture suggested a tuberculoid process.

The patient has been using 5 per cent "promin" jelly (sodium p,-p'-diaminodiphenylsulfone-N,N' didextrose sulfonate) on the oozing lesions since October 8. Many of the discharging sinuses have since dried.

DISCUSSION

DR. GEORGE C. ANDREWS: I was interested to see the improvement in this case. I have not used "promin" jelly for scrofuloderma, but have tried it for lupus vulgaris, without any benefit.

DR. MAURICE J. COSTELLO: I cannot understand how "promin" jelly worked in this case. Not a fraction of the diseased tissue came into contact with the jelly, unless it cleared up the surface of the eruption and then entered the sinuses.

DR. DAVID BLOOM: I should like to ask Dr. Wise whether he thinks that "promin," being a suflonamide drug, could probably have had a good effect on the secondary pyogenic infection and not on the tuberculous process itself?

DR. FRED WISE: I am unable to answer either Dr. Costello's or Dr. Bloom's questions. This is the first case in which I have had a spectacular result through the local application of "promin" jelly. Whether this was due to the elimination of secondary infection, I do not know. Improvement occurred in less than two weeks' time, and the patient had previously had other types of treatment that were ineffective. There is no doubt that treatment with "promin" jelly has been exceptionally effective in this case.

Generalized Progressive Scleroderma. Presented by DR. HERMAN SHARLIT.

A Case for Diagnosis (Lymphoblastoma? Neurodermatitis?). Presented by DR. MAX SCHEER for DR. JACK WOLF.

Arsenical Keratoses of Palms and Soles. Presented by DR. MAX SCHEER.

Chronic Exudative Lichenoid and Discoid Dermatosis Treated Successfully with Intravenous Injection of Typhoid and Parathyphoid Vaccine, Sunlight and Salt Water Bathing. Presented by DR. MAURICE J. COSTELLO.

S. B., a Jewish machinist, aged 43 and separated from his wife, claims that an eruption developed on his hands in December 1945, which he attributed to irritation from oil used in his work. He attended the New York Skin and Cancer Unit and was treated with salves, lotions, roentgen rays and penicillin in oil and wax, which, he claimed, intensified and spread the eruption. He was later sent to the Manhattan General Hospital, where he was treated for five weeks without improvement.

The eruption was generalized and extremely pruritic, consisting of small lichenoid papules, discoid dime-sized lesions, plaquelike areas, visible evidence of ferocious scratching, hyperpigmentation and thickening of the skin, enlargement of the lymph nodes and secondary infection.

There was a profound psychic element bordering on anxiety neurosis. The patient was hospitalized in June 1946, and he was given intravenous injections of typhoid and parathyphoid vaccine (nonspecific), which resulted in improvement but did not cause complete disappearance of his eruption. The latter was accomplished by subsequent daily prolonged sun and salt water baths at Coney Island, N. Y. He returned to work in the early part of September. There has been a slight recurrence of the eruption recently.

A biopsy by Dr. Wilbert Sachs unequivocally confirmed the diagnosis as presented.

DISCUSSION

DR. GEORGE C. ANDREWS: Unfortunately, summer is over, and there is recurrence of the itching and the eruption. I prophesy that within three or four weeks the eruption will be as bad as formerly. I had a patient in the office today

with the same disease. He goes to Florida, and his eruption clears up there; he comes back, and it recurs again. He has also improved with treatment with sulfapyridine, as some do for a time, and then there is recurrence. This man's improvement is gratifying, but I do not believe that it is going to be lasting. As. Dr. Rosen said, all patients do not improve with this simple treatment. I did not know of the patients who went to El Paso, but I did know of some who went to Arizona. They are fortunate in the benefit that they receive, because the eruption is otherwise incurable. I had a patient in Presbyterian Hospital for seven months who was helped by electric shock treatments, which cured him completely for three weeks. However, as soon as the effect of shock wore off, he began worrying again and began to scratch. The eruption is now as bad as ever.

Dr. Fred Wise: I believe that fever therapy with typhoid vaccine is good treatment for immediate relief, and I administer it to patients who can tolerate it without ill effects.

Dr. Herman Sharlit: There is no question about the diagnosis, but I agree with Dr. Andrews that the eruption is recurring. I have been impressed with the fact that the background in most of these cases is contact dermatitis. I think that in Cannon's paper lymphoblastoma-like eruptions from contact dermatitis included all these dermatoses. In some strange manner, when the patients get rid of the contact they get well. The patient I presented was sensitive to silk dyes. He was awarded compensation for his disease and then became well without leaving New York. That is why I ask whether any urticarial lesions have been present. When there are recurrences in my patient, he gets attacks of urticaria.

Dr. Anthony C. Cipollaro: It is gratifying to learn that some of the members of this society advocate treatment of pruritic eruptions of this type at health resorts. There is no doubt in my mind that salt water bathing and sunshine are good for these patients.

Dr. Maurice J. Costello: I think that this patient will have a recurrence; it is beginning now, but he was free of the eruption during the summer. He plans to buy an ultraviolet lamp, so that he can have generalized ultraviolet irradiation twice a week in his own home. Dr. Andrews mentioned that he has obtained results with sulfapyridine. I have had 2 or 3 patients on the wards at Bellevue Hospital whose eruptions cleared up completely with treatment with sulfapyridine. This is a compensation case. The eruption developed on the patient's hands while he was handling oil.

Erythrasma Showing Fluorescence. Presented by Dr. Maurice J. Costello.

S. A., a man aged 47, from the Bellevue Hospital Dermatology Clinic, presents two sharply demarcated velvety red areas in the inguinocrural regions. He had been unaware of their presence until they were called to his attention by the examining physician. The patient is presented mainly because of reddish gold fluorescence in the involved areas, which is apparent in examination under the Wood light. (Demonstration with the Wood light was carried out.)

MINNESOTA DERMATOLOGICAL SOCIETY

Louis A. Brunsting, M.D., *President*
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St. Paul, Nov. 1, 1946

A Case for Diagnosis (Hemangioendothelioma Recurrent After Surgical Excision?). Presented by Dr. Francis W. Lynch, St. Paul.

Multiple Carcinomas of the Skin in a Man Aged 43; Atopic Eczema Since the Age of 7, Treated at Times with Arsenicals. Presented by DR. FRANCIS W. LYNCH, St. Paul.

Sarcoidosis. Presented by DR. JOHN F. MADDEN, St. Paul.

Mrs. V. H., aged 31, was a ward maid on the tuberculosis wards at the Ancker Hospital from 1936 to 1943. In 1943 she noticed a pea-sized nodule on the lateral surface of the lower third of the left arm. This enlarged progressively until it was the size of an olive. A similar pea-sized lesion appeared on the left malar eminence in 1946. The lesions are painless, dark red and slightly elevated. The reactions to Mantoux tests were repeatedly 4 plus. The roentgenograms of the chest and long bones were normal. The sedimentation rate was 30 mm. per hour, and the serologic reactions to tests for syphilis were negative. The lesion on the arm did not respond to roentgen therapy. The patient's health is good.

Sarcoidosis. Presented by DR. FRANCIS W. LYNCH, St. Paul.

Mrs. F. F., aged 40, had a lesion of the left cheek for two and a half years. Her general health was good. When first seen eight months ago, she presented a reddish brown, elevated and infiltrated plaque 3/4 inch (about 2 cm.) in diameter, surrounded by an edematous halo having the appearance of groups of vesicles. Reactions of the blood to serologic tests were negative. Biopsy showed a sarcoid structure. The reaction to the Mantoux test was positive, with 1 mg. of tuberculin. The spleen was not palpable, and there was no lymphadenopathy. She was given superficial roentgen radiation (400 r), with slight improvement in the eruption.

DISCUSSION OF CASES OF SARCOIDOSIS

DR. HENRY E. MICHELSON, Minneapolis: A diagnosis of sarcoid may be made even with a positive Mantoux reaction. I think that all of us are willing to accept such a diagnosis on much broader microscopic observations than we used to. If the patient has sufficient insight, I see no reason for treating sarcoid. The clinical course is variable, but usually the patients get along well, and I believe that any cure is only a natural resolution of the disease. It is no surprise to me that long involvement, even though extensive, does not cause any symptoms. A recent review of tuberculosis in primitive groups has shown roentgenologically that there may be involvement without a single symptom.

DR. PAUL O'LEARY, Rochester, Minn.: Dr. Lynch's patient manifested "sago grain nodules," which twenty years ago were highly significant in the diagnosis of sarcoid but which are seldom mentioned today.

I am less pessimistic about the treatment of sarcoid than I formerly was and believe that chaulmoogra oil has therapeutic merit. Lomholt suggested its use because of the frequent histologic similarity to leprosy. Enthusiasm has been increased by the observation that in patients in whom the disease was of two or three years' duration the pulmonary lesions cleared rather rapidly following treatment with ethyl chaulmoograte, an ester of chaulmoogra oil. In about half of the patients with cutaneous sarcoids the same is true. It is the practice at the Mayo Clinic to start with 3 cc. given intramuscularly and in the cases of resistant disease to increase the dose to 15 cc. a day for approximately thirty injections. In an effort to temper some of this enthusiasm, a survey is now under way to estimate the incidence of and the average time for spontaneous involution of both the visceral and the cutaneous lesions.

Subacute Disseminated Lupus Erythematosus. Presented by DR. FRANCIS W. LYNCH.

Mrs. F. B. W., aged 49, first noticed a facial eruption in 1940. Examination then showed characteristic observations of chronic discoid lupus erythematosus, and the eruption responded promptly to a short course of treatment with bismuth subsalicylate in oil. During the next several years there was an occasional slight exacerbation of the eruption, once associated with iritis which had previously been present on a number of occasions. The eruption recurred about June 1, 1946, on the cheeks and subsequently extended to the arms and neck. It spread steadily to the present extent. Three years prior to presentation the patient submitted to an operation for the removal of both ovaries and tubes and the uterus. She felt well, but during the past six years she has been tired and nervous. The leukocyte count on two occasions has been 5,400 and 5,600. The hemoglobin is 80 per cent. The patient was given two injections of bismuth compound several weeks ago, and for the past two weeks she has received daily injections of 15 mg. of glutamic acid. She is presented to show the lack of favorable results from that treatment.

There is an extensive eruption of diffuse erythema associated with some slightly elevated papular lesions. The eruption involves chiefly the face, the exposed portion of the neck and chest and the exposed areas on the upper extremities, particularly on the extensor aspects. During the past several days there has been generalized itching, but no eruption had appeared at the time of the last examination.

DISCUSSION

DR. PAUL O'LEARY: I believe that this patient has a mild type of dermatomyositis and not disseminated lupus erythematosus. She had decided reduction in muscle strength in the arms, shoulder girdle and back. In addition, there is obvious atrophy of these muscle groups. The present distribution of the cutaneous lesions is as typical for dermatomyositis as it is for disseminated lupus erythematosus; however, the same does not apply to the morphologic aspects. The pathologic observations of the cutaneous lesions of dermatomyositis are those of toxic erythema, while I believe that the observations in lupus erythematosus, as described by Montgomery, are classic. Confusion exists because the morphologic features in the late stages of both diseases are similar, in that atrophy with some erythema remains while the diagnostic aids which are so helpful in the differential diagnosis are overlooked. In dermatomyositis the patient has, as a rule, mild leukocytosis, a normal or slightly increased sedimentation rate, a high creatinine rate, seldom any rise in temperature and localized muscle tenderness, which may become generalized. In disseminated lupus erythematosus leukopenia, a high sedimentation rate, fever and joint pains or arthralgia, rather than muscle pains, in addition to the classic renal and cardiac lesions, are present. There may be remission in both diseases when the differential diagnosis becomes difficult, because the laboratory aids may not be characteristic. If only the cutaneous lesions are considered, an accurate differential diagnosis may not be possible.

DR. HENRY E. MICHELSON: The moment one becomes aware of dermatomyositis, one encounters more cases. Although one sees them fairly well advanced, I would like to know more about the onset and the acute stage. I have been disappointed in the results of muscle biopsies and believe that we should all agree to take the biopsy specimen from a particular muscle in a fixed place, so that there might be some uniformity of observation. I also believe that muscle biopsies should be made in acute lupus erythematosus, so that there may be obtained some information in that field.

DR. PAUL O'LEARY: Muscle biopsies have been disappointing in the experience of the Mayo staff, because it has not been possible to recognize a classic histologic muscle picture of dermatomyositis. This is due to the fact that the observations vary from those of acute inflammatory myositis to almost complete muscle destruction. A single estimation of creatine and creatinine is likewise not significant in patients with dermatomyositis. In order to make such tests authentic, it is necessary to know what the creatine and creatinine levels were before the muscle disease developed, in addition to establishing the levels while the patient is on a restricted, a limited and a full diet.

Dermatomyositis with Calcification. Presented by DR. JOHN F. MADDEN, St. Paul.

DISCUSSION

DR. PAUL O'LEARY: Rochester, Minn.: Calcinosis cutis is a common complication in the arrested phases of dermatomyositis, in both children and adults. The calcium deposits are prone to appear at sites of trauma, such as the knees, elbows and knuckles, although they may appear any place. I do not believe that all of these calcium deposits are the result of degeneration of muscle or skin; no doubt the inability to utilize the calcium ingested is a more plausible explanation than that of degeneration.

DR. F. AKWARI, Bagdad, Iraq (by invitation): It is my impression that lupus erythematosus and dermatomyositis are the same. It is difficult to say. In my country one seldom sees either of these diseases.

Granuloma Inguinale. Presented by DR. JOHN F. MADDEN, St. Paul.

Onychomycosis (Trichophyton Purpureum). Presented by DR. RODNEY F. KENDALL, St. Paul.

Mrs. M. G., aged 25, was first seen July 10, 1946, complaining of deformity of the great toe nails, of a year's duration. Examination shows crumbly striated nails of the great toes. The skin of the feet is normal.

Culture on Sabouraud's medium showed pure culture of Trichophyton purpureum.

DISCUSSION

DR. STURE JOHNSON, Madison, Wis. (by invitation): Clinically the nail involvement is due to Trichophyton purpureum. The culture which is available is that of T. purpureum, which often invades the toe nails as well as the finger nails. A search for other evidence of tinea of the foot yielded negative results. Getting a positive culture is commendable, since contamination so often hides or prevents the growth of the pathogen. Purpureum infections of the nail are difficult to treat. Lately I have been using an ointment containing undecylenic acid, particularly for tinea of the feet, with good results. When it is used on the nail, one does not get sufficient penetration. When there is decided nail involvement, avulsion of the nails followed by chemotherapy is indicated. It is unusual to see this type of nail involvement in a female subject, unless she has been around gymnasiums and shower rooms. The patient has never had vesicles.

DR. E. D. DELAMATER, Rochester, Minn. (by invitation): I do not believe that it is possible to distinguish clinically between cases of onychomycosis (tinea unguium) caused by T. purpureum from those caused by Trichophyton gypseum and other members of the genus, including that member causing favus. In addition, it is frequently extremely difficult to identify the organisms isolated in these

diseases. Identification of the dermatophytes is still not a simple straightforward procedure and is complicated by many factors.

I believe that you have all seen the collection of variants of Trichophyton gypseum, growth of which was induced by ultraviolet rays, which Dr. Emmons has sent me. One or two of these variants are similar to T. purpureum, and the suggestion is strong that such induced variants may give the key to the genetic origin of the types or even species of these fungi. Recently I have been able to isolate numerous spontaneous variants from a single mutable strain. This also strengthens the suggestion.

Sabouraud and, more recently, Lewis and Hopper and their associates have called attention to the type of tinea pedis which they consider to be produced typically by T. purpureum. During this last summer (1946) I have had several cases of this type, from which I have isolated characteristic colonies of Trichophyton mentagrophytes (gypseum). I would, therefore, tend to question whether a particular type of lesion is always caused by a specific morphologic species of trichophyton. I would like to raise the question as to whether the organisms in cultures of T. gypseum and T. purpureum obtained from the feet, as well as from other areas, are not perhaps genetic variants of a common type.

It has been well established in plant pathology that genetic variants are capable, not only of decided morphologic differences from one another, but also of change in fundamental physiologic processes. Certainly, further work on the fungi of medical importance with this in mind is indicated and may be extremely fruitful.

Concerning treatment, Dr. Johnson has emphasized the difficulty in treating these diseases. It appears to be necessary to remove the infection either by surgical treatment or by use of some drug. Whether the nail is scraped, removed with a dental burr or surgically excised, the infecting organism is eliminated. Dr. Ormsby has emphasized the usefulness of removal with the dental burr. As a routine procedure patients at the Mayo Clinic are trained to scrape away the infected parts with a sharp instrument and simultaneously use some fungicidal ointment.

Concerning the treatment of so-called T. purpureum infections of the feet, I would like to suggest that the resistance of these infections to treatment is not necessarily due to the particular type of organism involved, but rather to the hyperkeratotic character of the lesions themselves. Keratin is a notoriously inert chemical substance, as Dr. Rothman has emphasized, and is difficult to penetrate. It would seem that until substances, better than Whitfield's ointment, are found that will penetrate keratin and at once have a fungicidal action, treatment of the disease will be difficult. I believe that when understanding of the causative organisms is based on a firm fundamental biologic fundation, and treatment is based on a knowledge of the chemical and physiologic nature and activity of the skin, progress in the treatment of these diseases will be made.

Ichthyosis Hystrix. Presented by DR. JOHN F. MADDEN, St. Paul.

J. S., a girl aged 4, was first seen to have warty excrescences along the lateral aspects of her left ankle and the left side of her chest when she was 9 months old. Examination reveals a skin-colored warty plaque extending from the lateral side of the left ankle to the thigh and a similar band on the left side of her chest.

DISCUSSION

DR. STEPHEN EPSTEIN, Marshfield, Wis.: I was wondering whether this is not a nevus unilateralis, as it is unilateral. Ichthyosis hystrix usually occurs on both sides.

DR. CARL LAYMON, Minneapolis: The question of localized forms of ichthyosis is a difficult one and as yet has not been fully decided. Ichthyosis hystrix, palmar and plantar keratoses and verrucous nevi are included in this group of anomalies of cornification. It would seem preferable from the standpoint of simplicity, however, especially until more is known about them, to group them all under the broad heading of ichthyosis.

Lymphocytoma Miliare Faciei. Presented by DR. STEPHAN EPSTEIN, Marshfield, Wis.

The patient noted small papules on the tip of the nose for about six months. They seemed to be spreading slowly from the nose onto the cheek. Itching is present; no dermatitis preceded the eruption. Six years prior to presentation the patient had small tumors on the side of the nose, which were removed at that time.

Examination reveals three or four scattered pale waxy papules. They are located over the anterior bridge and tip of the nose. The blood cell count was as follows: hemoglobin 13.1, erythrocytes 4,500,000 and leukocytes 13,200, with 68 per cent polymorphonuclear leukocytes, 22 per cent lymphocytes, 4 per cent eosinophils, 5 per cent monocytes and 1 per cent basophils.

The microscopic sections showed a well defined tumor-like nodule in the upper and middle parts of the corium. This node consists of lymphoid tissue, mainly small lymphocytes, but contains large germinal centers with a few mitoses (pathologic report by Dr. Herman Pinkus). The clinical and histologic diagnosis is that of benign lymphocytoma.

DISCUSSION

DR. STEPHAN EPSTEIN, Marshfield, Wis.: Lymphocytomas are benign lesions. They are not of the leukemic type. This is a typical case. One could see some of the translucent brownish nodules which, as Dr. O'Leary has mentioned, are sometimes seen in sarcoidosis. In addition to these "miliary" lesions, larger tumors may occur of the same size and color as Boeck's sarcoid. The favored location is the face, especially the nose and cheeks.

They respond to relatively large amounts of radium and roentgen therapy. They recur, however, and some have been observed for over ten years without having developed into lymphoblastoma.

A Case for Diagnosis (Necrobiosis Lipoidica Diabeticorum?). Presented by DR. JOHN F. MADDEN, St. Paul.

DISCUSSION

DR. PAUL O'LEARY, Rochester, Minn.: All ulcers on the legs in the so-called stasis area are not necessarily due to varicosities or old thrombophlebitis, as some of these are the results of hypertension and associated arteriosclerosis. They are "anemic ulcers," but may be due to arteriosclerosis rather than venous or lymphatic disease.

DR. STEPHAN EPSTEIN, Marshfield, Wis.: I think that it is an important point, because once one recognizes that these ulcers are not stasis ulcers, then one realizes that the prognosis is worse than that for stasis ulcers.

Nonsuppurative Panniculitis. Presented by DR. JOHN F. MADDEN.

Mrs. H. D., a nurse aged 50, stated that deep-seated painful nodules appeared on the lateral surface of the shoulders in 1942. Some of the lesions were preceded by fever and general body aches and pains. She now has deep-seated olive-sized

nodules on the shoulders, arms and flanks. Some of the lesions are adherent to the skin and pull it down, producing a puckered appearance. None of the lesions have ulcerated, but the skin over some is bluish purple while there is no change in the color of the skin over others. None of the old lesions have disappeared, but new ones have occurred at intervals. The patient had 2,400,000 units of penicillin, with no effect.

DISCUSSION

DR. STURE JOHNSON, Madison, Wis. (by invitation): This patient stated that she was given alum-precipitated toxoid for diphtheria. I wonder whether this might have been a factor in the cause of panniculitis, since the lesions occurred shortly afterward.

DR. STEPHAN EPSTEIN, Marshfield, Wis.: Several months ago I saw a baby in whom severe induration of the cheeks developed following injection of alum-precipitated diphtheria toxoid. A lesion developed at the site of injection and on both cheeks. The patient presented here gave, also, a history of indurated nodules following injections of toxoid.

DR. STURE JOHNSON: It is a guess on my part that the toxoid played a role in the panniculitis.

Psoriasis; Arsenical Keratoses. Presented by DR. JOHN F. MADDEN.
Addison's Disease. Presented by DR. FRANCIS W. LYNCH, St. Paul.

Mr. H. O., 19 years old, has been known to have diabetes for the past eight years. This has been well controlled by treatment. About April 1946, he first noted weakness, anorexia and loss of weight which have continued to increase in severity; he lost 30 pounds (about 13.6 Kg.). There has also been progressive anemia. He was recently hospitalized for an operation for acute appendicitis. During his stay in the hospital he was observed to have a persistently increased sedimentation rate. The blood pressure varied around 110 systolic and 80 diastolic. The liver and spleen have not been palpable. Examination of the urine showed no melanin or hemosiderin. Cutaneous biopsy showed an abnormally large amount of melanin, but no iron was evident even with special staining. The oral administration of sodium chloride resulted in some relief from the weakness and general discomfort. A test for water concentration and secretion led to results characteristic of Addison's disease.

The Mantoux reactions was negative, and roentgenographic study of the chest showed no tuberculosis. Generalized pigmentation began insidiously and gradually progressed.

Examination shows diffuse brown hyperpigmentation with a slightly yellow tint. Several areas of vitiligo surround small pigmental nevi. There is some brown hyperpigmentation of the buccal mucosa near the angles of the mouth.

DISCUSSION

DR. F. W. LYNCH: I presented this case because of the association of diabetes with other grandular disturbances. In recent numbers of the *Journal of Clinical Endocrinology* there are reports of Addison's disease in young patients associated with disturbances other than tuberculosis. It is not frequently encountered.